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CHRONIC DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS*

BY

J. G. SCADDING, M.D., F.R.C.P.

Director of Studies, Institute of Diseases of the Chest, Brompton Hospital, London

The name "chronic diffuse interstitial fibrosis of the lungs" indicates a condition defined in morbid anatomical terms. Literally and without restriction it could be applied properly to a wide range of conditions, some of which would normally be included in other diagnostic categories. For instance, the late stage of sarcoidosis, widespread chronic pulmonary tuberculosis, dust diseases of the lung, and the end-results of some chronic inflammatory changes include an element of interstitial fibrosis; though in many of them the changes in the interstitial tissue are not widespread or predominant. If we exclude cases which can reasonably be included in one of these diagnostic categories we shall be left with a group in which widespread lung changes characterized by the progressive development of fibrosis in the interstitial tissue of the lung cannot be explained as the result of an otherwise recognized pathological process. It is this group which I shall discuss. Though it seems unlikely that all the cases in the group so defined are due to the same cause, experience shows that at least a large proportion of the group is constituted by cases which present a syndrome recognizable with confidence on clinical, radiological, and physiological features.

In order to put certain matters of terminology into perspective, reference must be made first to a group of cases described as "acute interstitial fibrosis of the lungs" by Hamman and Rich (1944). These four cases were all in young adults. They ran an acute course with fever, the total duration of the disease from onset to death from right ventricular failure ranging from six weeks to six months. In none of them was clubbing of the fingers recorded. Histologically they were characterized by the following changes. In the alveoli there was some oedema, with red blood cells and a few leucocytes and enlarged epithelial cells. Some alveoli were lined by a hyaline membrane. In places there was necrosis of alveolar and bronchiolar walls. There was extensive progressive proliferation of fibrous tissue in the interstitial tissue. In places the alveolar contents were undergoing organization. In three out of four cases there was an excess of eosinophils in the interstitial tissue. Thus, the syndrome described by Hamman and Rich was both pathologically and clinically an acute process.

Present Series

The more chronic type of diffuse interstitial fibrosis of the lungs which is the present subject of discussion is in my experience, and also judging from the cases reported in the literature, much more frequent than the acute type described by Hamman and Rich. I have had 26 cases under my own care in the past eight or nine years up to the beginning of the year 1959. These 26 cases were equally divided between the two sexes. They were in an older age-group than the acute cases of Hamman and Rich. Their ages at the onset of symptoms ranged from 23 to 68 years, with a mean of 53½ years; only three of them were under the age of 50. We obtained direct histological evidence in 13 of these. The other 13 conformed so closely to all aspects of the typical picture which I shall describe that I felt justified in including them in the group, more especially since in no case in which I have been confident of this diagnosis has it been disproved by subsequent histology, either biopsy or post-mortem.

The typical clinical history in this more chronic type starts with the leading symptom of gradually increasing breathlessness on exertion. This dyspnoea may take quite a long time to develop to a degree which constitutes a serious disability. Several of my patients had noticed increasing breathlessness for two to three years before they consulted a doctor for the first time about it. The patients have a cough, which, though generally either dry or productive of only a little nondescript mucoid expectoration, may be troublesome. They, like everyone else, are liable to intercurrent respiratory infections, which may cause the sputum to become purulent because of secondary bacterial infection; but this is incidental and not part of the typical picture, and may be controlled by suitable antibacterial treatment. Clubbing of the fingers may be an important symptom. I call it a symptom because some of my patients have complained of it, and one noticed the change in the shape of her fingers several years before she became breathless. In other cases clubbing ranks only as a sign, found on physical examination. At the time of my first examination clubbing was classified as severe in seven, moderately severe in eight, slight in five, and absent in six; in two of the latter it developed later under observation. It usually assumes the classical drumstick form. I have not observed pulmonary osteoarthropathy in any of these cases. Cyanosis is invariable in the moderately advanced disease, and at this stage is evident even at rest, becoming deeper after exertion. Earlier in the disease, at a stage when they are not yet cyanosed at rest, patients may become cyanosed after exercise.

Physical examination shows signs which in most cases make an important contribution to diagnosis. First, the patient may be seen to be cyanosed, especially after exercise, and the fingers may be clubbed. As he lies at

*An open lecture given at the Institute of Diseases of the Chest on June 3, 1959.

rest on the couch, hyperventilation may be sufficient to be noticed as a clinical sign. On examination of the chest there are characteristic showers of fine-to-medium rales during inspiration over the lower parts of the lungs, extending upwards to a variable level, and persisting after cough and at repeated examinations. In some cases, where the changes are predominantly basal, there may also be found impairment of percussion note and alteration of breath sounds towards a bronchial quality over the bases of the lungs at the back of the chest.

This combination of symptoms and signs constitutes a striking clinical picture; and a middle-aged or elderly person who, having previously been well, complains of progressive dyspnoea on exertion over the preceding few years, has a cough perhaps troublesome but usually unproductive, may be cyanosed especially after exercise, has gross clubbing of the fingers, has rales at the bases of the lungs, has no obvious cardiac abnormality, and is not constitutionally ill, can be suspected with some confidence of suffering from chronic diffuse interstitial fibrosis of the lungs.

Physical and Radiological Findings

The physiological picture correlates well with the clinical and morbid anatomical picture. The changes are mainly those of a defect of diffusion between the alveolar air and the alveolar capillaries. At first the ventilatory function is relatively little reduced and may be normal. The total lung capacity is usually somewhat reduced, with a proportionate reduction in its subdivisions, presumably from reduction in the volume of the peripheral air-spaces by the thickening of the alveolar walls. In spite of this, the maximum voluntary ventilation may at first be within the normal range. The volume expired in the first second of a forced expiration, which correlates well with maximum voluntary ventilation, is also normal, and constitutes the normal proportion (more than 70%) of the total forced vital capacity, indicating that airway obstruction plays no part in the dyspnoea. Whereas a normal adult has a resting ventilation of no more than 7–8 l./min., these patients may be ventilating even at rest at 15–16 l./min., and on exercise they hyperventilate even more, so that the ventilatory cost of exercise is high. Their arterial oxygen saturation is reduced, in the earlier stages only after exercise, but later at rest and even further after exercise.

The arterial carbon-dioxide tension is normal or even low. Appropriate tests will show reduction in diffusing capacity of the lungs. The test most commonly used is the uptake of carbon monoxide, which is much reduced even in the earlier stages. The combination of a reduced carbon-monoxide uptake with a normal or only slightly reduced ventilatory function leads inescapably to the conclusion that there is a serious defect of diffusion across the alveolar membrane. This physiological picture has been described as alveolo-capillary block or alveolar respiratory insufficiency (Baldwin, Cournand, and Richards, 1949). Later in the disease the ventilatory capacity becomes reduced, with progressive reduction in maximum voluntary ventilation and in volume expired in one second, and there may be secondary changes suggestive of emphysema—that is, of dilatation of peripheral parts of the air passages, in the form of an increase in the proportion of the total lung capacity which constitutes the residual capacity.

Radiologically the chief features are shadowing of nodular or reticular pattern predominantly at the bases but also sometimes extending throughout the lungs, involving both lungs but not necessarily symmetrically. The quality and distribution of these changes is rather variable from case to case, as is discussed below.

The course of these chronic cases is usually slowly downhill, but some patients seem to have quite prolonged remissions of progression of the disease. By this I mean that the disease sometimes ceases to progress and the patient remains at a steady level of disability for a number of years.

The first two cases illustrate the more chronic type, and the third an acuter type of the disease.

Case Reports

Case 1.—A clergyman aged 69, whom I first saw in February, 1951, had been becoming increasingly breathless on exertion for four years. His only other symptom was a cough which produced about 15 ml. of mucoid sputum daily. On examination I noted cyanosis, gross drumstick clubbing of the fingers, and constant rales at the bases of both lungs. Fig. 1 shows the radiographic appearance of the lungs, with coarse mottling giving a somewhat honeycombed appearance, mainly at the bases. Physiological studies showed a total lung capacity of 4.4 l., considerably less than the expected figure, with a residual capacity of 1.9 l., constituting a normal proportion of the total lung capacity, and a maximum breathing capacity of 103 l./min.,

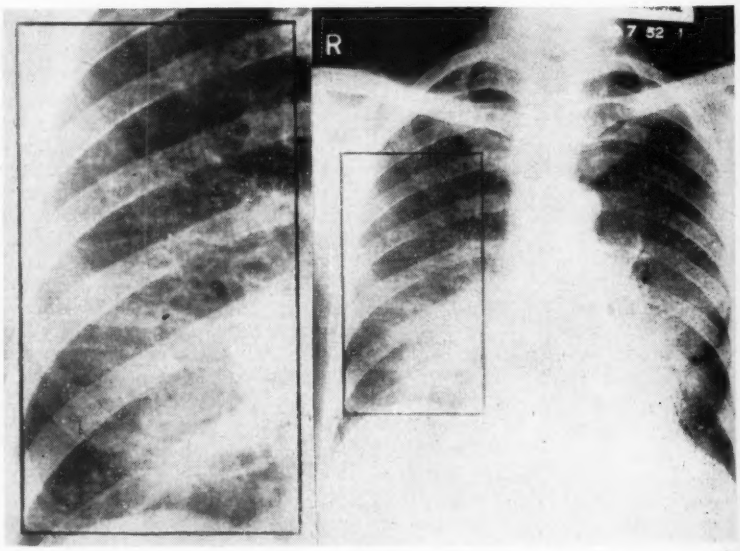

FIG. 1.—Case 1. Radiograph of chest. The area outlined is shown on a larger scale for detail.

well within the normal range for a man of 69. The ventilation at rest was 15 l./min.—a high figure—and the arterial oxygen saturation was only 86% at rest and fell to 65% on exercise. This patient received only simple symptomatic treatment. He survived for a total period of seven years from the beginning of his symptoms and died in February, 1954, at the age of 72 as a result of an intercurrent respiratory infection. During the last three years of his life there was little change in the severity of his symptoms.

Case 2.—This patient, a housewife, was aged 57 when I first saw her in 1954. Since January, 1953, she had been feeling tired and breathless and had lost a little weight. When I first saw her about the beginning of 1954 she was afebrile and had clubbing of the fingers, which she herself had noticed to be coming on for a few months. There were fine rales at the bases of both lungs. Radiologically there was a diffuse, rather fine mottling at the bases of the lungs, more on the left than on the right (Fig. 2). A lung biopsy showed thickening, increased cellularity and fibrosis of the alveolar walls, with some mononuclear exudate and rather prominent epithelial cells in some of the alveoli. She has been observed for six years from the onset of the

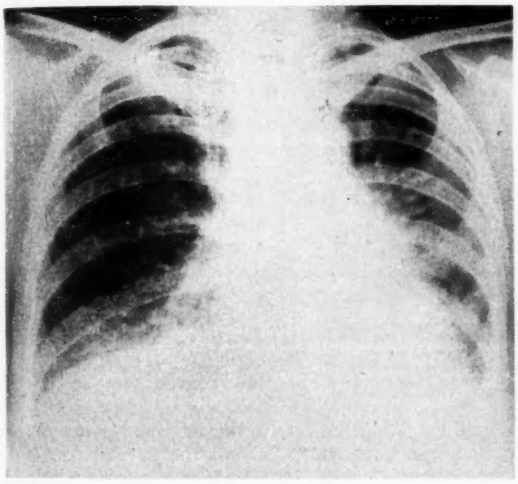

FIG. 2.—Case 2. Radiograph of chest, January, 1954.

symptoms and 5½ years from the biopsy, with only occasional symptomatic treatment. She is still breathless on exertion, has clubbed fingers, but is carrying on and seems no worse over the past few years. Radiologically there has been progression of the changes to honeycombing throughout the left lung and possibly also at the base of the right lung (Fig. 3).

Three of my 26 cases might be regarded as intermediate between the very chronic type, of which Cases 1 and 2 are examples, and the acute type described by Hamman and Rich; but all three of these patients still survive for periods ranging from 1½ to 4½ years from the beginning of their symptoms. Their ages when their illnesses began were 25, 40, and 50 years; the younger two were the youngest in the whole series of 26 patients.

Case 3.—A 50-year-old housewife, when I first saw her in September, 1957, had noticed for four months rather rapidly increasing breathlessness and a slight unproductive cough. She was afebrile. The fingers were slightly clubbed, and constant rales were audible at the bases of both lungs. Radiologically there was a rather featureless shadowing over the lower half of both lungs which closer inspection showed to be made up of a very fine nodular pattern (Fig. 4).

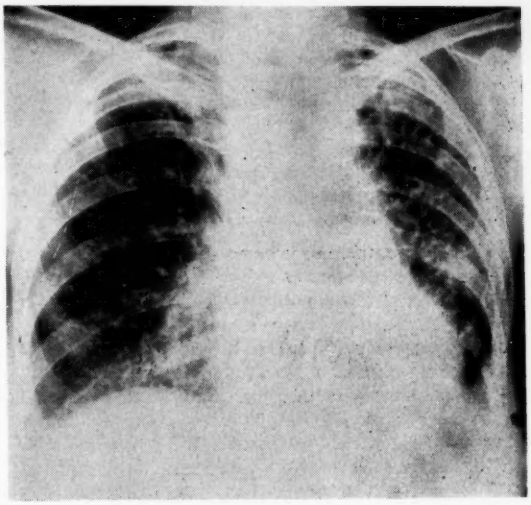

FIG. 3.—Case 2. Radiograph of chest, November, 1958. "Honeycombing" has developed in the left lung.

Lung biopsy showed great thickening of the alveolar walls with a great increase in reticulin and a considerable amount of actual fibrous tissue, and some mononuclear and epithelial cells in the alveoli. Physiologically the pattern of deranged function was characteristic, with a moderately reduced maximum voluntary ventilation of 57 l./min., and a carbon-monoxide uptake of 5.7 ml./min./mm. Hg, less than half the lower limit of the normal range. The disease was progressing rather rapidly, and for this reason she was treated with prednisolone. This is the only case in the whole series in which there is evidence of something approaching a remission from the use of a corticosteroid, persisting after withdrawal of the hormone. After two weeks' treatment with 30 mg. of prednisolone daily there was substantial clearing of the radiographic shadows with considerable symptomatic relief. The dosage of prednisolone

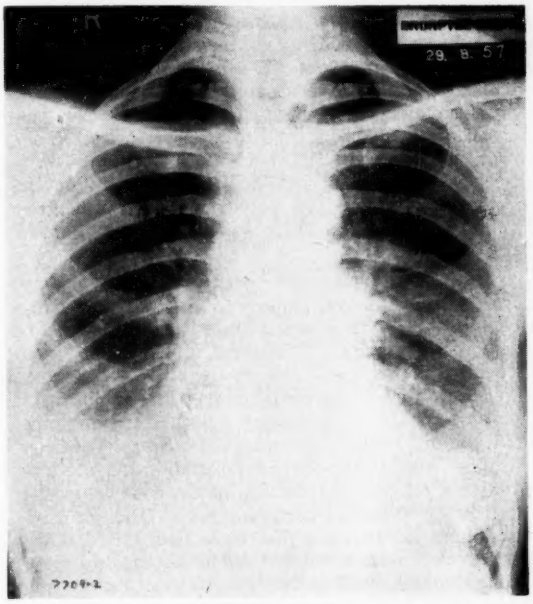

FIG. 4.—Case 3. Radiograph of chest, August, 1957.

was gradually reduced, and after over a year's treatment with 15 mg. daily the drug was withdrawn gradually in February, 1959. To date (June, 1959) the symptomatic and radiographic remission has been maintained. But the diffusing capacity for carbon monoxide has improved only slowly, up to 7.1 and later up to 10.9 ml./min./mm. Hg, still well below the normal range.

Histology

The essential features of the histology of these more chronic cases can be quite briefly stated. Within the affected alveoli there may be some mononuclear exudate and proliferation of lining cells, which may fill some of them. The alveolar walls are thickened with chronic inflammatory cells, fibroblasts, and young fibrous tissue, and suitable staining shows considerable reticulin proliferation. Other changes in the alveoli, such as hyaline membrane, organization of exudate, and the presence of eosinophils, have been described, but are inconstant, and if present may not be prominent. In the late stages the fibrous tissue in the more affected parts of the lung condenses down, so that the lung presents a honeycombed appearance, in which completely destroyed and condensed lung tissue contains cyst-like air-spaces which are all that is left of the respiratory part of the broncho-pulmonary tree. At this late stage the hypertrophy of the cells, possibly of bronchiolar origin, which line the air-spaces may in places become exuberant to form several layers of hypertrophic epithelium. This gives rise to an appearance closely resembling that produced in the alveoli by the so-called pulmonary adenomatosis or alveolar-cell carcinoma. In one patient changes of this sort were found at necropsy in at least three lobes.

In one of my patients there were changes in the liver of rather unusual character, which do not seem to have been reported previously. This was a woman aged 41, who, when I first saw her in January, 1958, had been becoming progressively more breathless on exertion for one year. In the chest radiograph there was fine mottling over both lungs, mostly at the bases. A lung biopsy showed characteristic changes of interstitial fibrosis, with typical thickening of the walls of the alveoli, which contained epithelial cells and mononuclear cells. Because sarcoidosis had been suspected before she was referred to me a liver biopsy had been performed. This showed normal liver cells, but the portal tracts were densely infiltrated with lymphocytes, some histiocytes and fibroblasts, and a few polymorphonuclear neutrophils and plasma cells. There was some formed fibrous tissue.

It is of interest that the sister of another of my patients, Case 3 above, came into hospital under my care in 1954 with an obscure illness of which hepatomegaly was a feature. Exhaustive investigation failed to elucidate the nature of this illness, but a liver biopsy showed infiltration of the portal tracts with a nondescript granuloma of similar character. Both the symptoms and the granulomatous change in the liver have been controlled with continued administration of corticosteroids but relapse on reduction of the dose below the equivalent of 50 mg. of cortisone daily. Though there is at present no evidence that these liver changes are related to interstitial fibrosis of the lungs, I record these two observations, because they may at some future time be seen to fit into a pattern at present not evident.

Radiology

I have already mentioned that the radiographic appearances are variable. Fig. 5 shows a coarse mottling fairly uniform throughout the lungs of a man aged 63, in whom the diagnosis was confirmed histologically after death. Fig. 4 (Case 3) shows a much finer mottling, again fairly uniformly distributed, which might perhaps be described accurately as stippling. Fig. 2 (Case 2) shows a very fine stippling giving a rather cloudy appearance involving predominantly the

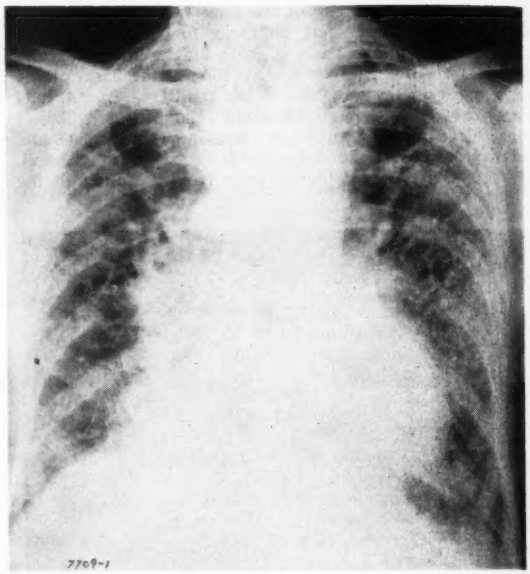

FIG. 5.—Radiograph of chest of a man aged 63, showing coarse type of mottling due to diffuse interstitial fibrosis.

bases of the lungs, especially the left, and proceeding over the course of four years to the development of "honeycombing" (Fig. 3). Fig. 1 shows a mottling of intermediate character, mainly in the middle and lower zones of the lungs, with some early "honeycombing."

Chronic diffuse interstitial fibrosis of the lungs shares with other conditions causing fibrosis at and beyond bronchiolar level some interesting bronchographic appearances. The bronchi seem to maintain an undiminished calibre much further out towards the periphery than usual, and the peripheral zone up to 5 mm. wide which normally remains unfilled is much narrowed. These appearances are shown in Fig. 6, which may be compared with the normal, shown in Fig. 7. Reid and Simon (1958) have shown that this unfilled peripheral zone represents the lung tissue beyond terminal bronchiole level. The bronchographic appearances in interstitial fibrosis of the lungs thus seem to be due to the condensation of the respiratory part of the broncho-pulmonary tree, which is evident pathologically in the later stages of this disease.

Aetiology

Various possibilities have been advanced in discussions of the causation of "idiopathic" diffuse interstitial pulmonary fibrosis. It has been suggested that the acute cases might be a response to some form

of chemical irritant. We know that exposure to nitrous fumes, for instance, may produce not only an acute illness with pulmonary oedema, but sometimes also the gradual development of a condition which has been described as "bronchiolitis fibrosa obliterans" with fibrosis in the peripheral parts of the lungs. The analogy is very imperfect, since bronchiolitis is not a feature of chronic interstitial fibrosis. Nevertheless the hypothesis that a fibrosis of this sort might be a response to a chemical irritant must be considered. It can be rejected both because of the absence of a history of exposure to chemical irritants and because there is usually no acute episodes at the beginning of the chronic illness. None of my patients has been engaged in an occupation involving any evident risk.

The possibility that diffuse interstitial fibrosis might be the result of some sort of chronic viral infection has been considered. But against this there is the fact that in viral pneumonias the greatest damage is at bronchiolar level. Delayed resolution of an acute pneumonia, especially a viral pneumonia, has been considered, but seems unlikely in view of the absence of an initial acute stage; and it seems inconceivable that any such process could occur so widely as to produce changes as generalized as those of chronic diffuse interstitial fibrosis. Moreover, in delayed resolution of acute pneumonia there is intra-alveolar organization with the characteristic appearance of fibroblasts growing through the interalveolar pores, which is not paralleled in chronic interstitial fibrosis.

The resemblance of some aspects of the chronic fibrosing changes that may occur in the lungs of hypertensive patients who have been treated for a long time with hypotensive drugs has been noted. The resemblance here is, I think, fortuitous. In the "hexamethonium lung" the most prominent change appears to be intra-alveolar organization of fibrin-rich oedema, and interstitial fibrosis is less constant and less prominent.

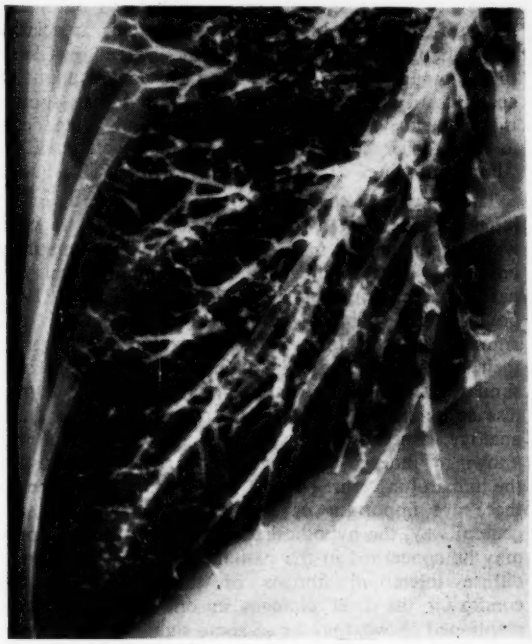

FIG. 7.—Normal bronchogram for comparison with Fig. 6.

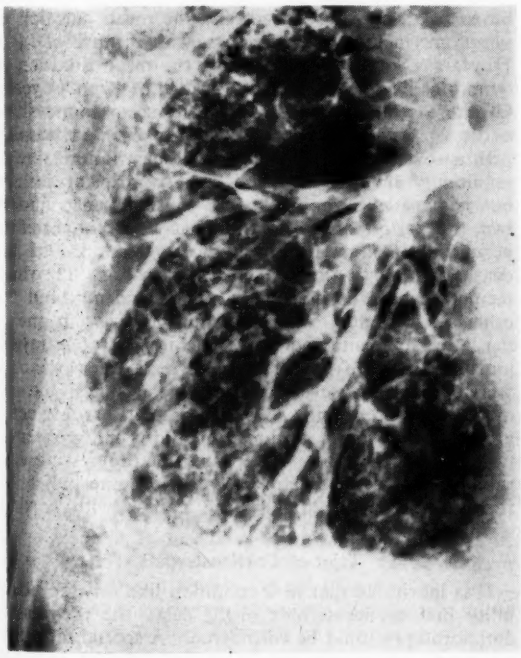

FIG. 6.—Bronchogram in a patient with chronic interstitial fibrosis of lung, showing great condensation of peripheral part of bronchopulmonary tree and diminution of normal peripheral unfilled zone.

Andrews (1958) has described an interstitial fibrosis of the lung caused by obstruction of pulmonary veins, with some features resembling those seen in "idiopathic" interstitial fibrosis; but in the many reported cases of the latter condition in which necropsy has been performed no venous obstruction has been mentioned.

The possibility of a relationship with the so-called collagen diseases must next be considered. A number of cases have been recorded in which lung changes indistinguishable from the description given above have accompanied typical rheumatoid arthritis. Rubin and Lubliner (1957) in their survey of 15 personally observed patients included one who also had rheumatoid arthritis. I have observed three patients with rheumatoid arthritis who had lung changes, confirmed histologically in two, indistinguishable from those of diffuse interstitial fibrosis; these three are not included in the 26 on which my main description is based. I have excluded them because they are distinguished from the main group not only by the presence of rheumatoid arthritis but also by a positive Rose–Waaler differential sheep red-cell agglutination test. In all my patients with chronic interstitial fibrosis without rheumatoid arthritis in whom this test has been carried out it has been negative. There is thus not only clinical but laboratory evidence differentiating between these two groups.

In scleroderma with visceral manifestations—better called progressive systemic sclerosis—changes may develop in the lungs which are not very dissimilar from

those of chronic interstitial fibrosis; but their predominantly basal distribution and their association with changes in the skin and the oesophagus serve to distinguish them clinically. Moreover, published accounts of their pathology suggest that they show a more exclusively fibrotic character and a tendency to the earlier and more prominent development of "honeycombing" (Orabona and Albano, 1958).

The suggestion that diffuse interstitial fibrosis of the lungs may be related to the collagen diseases, together with recent interest in the problems of auto-immunity, has led to speculation whether auto-immunity plays a part in the pathogenesis of this syndrome. Read (1958) prepared in rabbits an anti-rat-lung serum, and administered this to rats. This produced changes in their lungs which, examined serially, were remarkably similar histologically to those observed in the human disease, diffuse interstitial fibrosis. Argument by analogy, especially from the rat lung, which is well known to undergo pathological changes very readily, to the human lung must be used with caution; nevertheless these are important observations, and support, in a general way, the hypothesis that a tissue auto-immunity may be concerned in the pathogenesis of "idiopathic" diffuse interstitial fibrosis of the lungs. In this connexion the liver changes in one of my patients, mentioned above, may be of some significance; Luxton and Cooke (1956) have reported liver changes in Hashimoto's disease of the thyroid, a condition in which the importance of auto-immunity has been established.

Differential Diagnosis

Most of the types of widespread fibrosis which may be caused by recognizable agents can be distinguished from "idiopathic" diffuse interstitial fibrosis on consideration of the total clinical, radiological, and physiological picture. Among these, dust diseases may cause confusion in all respects save the occupational history; clubbing is rare in most industrial lung diseases, but may be prominent in asbestosis. Sarcoidosis should be distinguished without much difficulty; in sarcoidosis, dyspnoea is associated with the late fibrotic stage when usually there is local contraction of fibrous tissue, most often into the middle zones of the lungs, with emphysema at the bases and at the apices, an appearance quite unlike that seen in interstitial fibrosis. As a generalization it may be said that in sarcoidosis radiographic shadows in the lungs precede and in the early stage are out of proportion to dyspnoea, whereas in interstitial fibrosis dyspnoea in the early stage is out of proportion to the radiographic changes. Moreover, clubbing is usually absent in sarcoidosis, and very rarely even of moderate degree. Typical histological changes may be found in easily accessible tissues such as lymph nodes, skin, or liver.

Differential diagnosis from the lung changes which may occur in some of the collagen diseases may in some instances be largely a matter of definition of terms. The relevant practical points are mentioned above in the discussion of aetiology.

It may be difficult to differentiate between diffuse interstitial fibrosis and the various forms of "honeycomb lungs" (Oswald and Parkinson, 1949). This is a convenient general term for a group of cases characterized by widespread formation of small cysts in the terminal parts of the bronchopulmonary tree. Such changes, throughout the lungs, may be associated with two general systemic diseases—mesodermal dysplasia, of which tuberous sclerosis, adenoma sebaceum, and subungual fibromata are other detectable features (Dawson, 1954), and non-cholesterolaemic xanthomatosis, of which eosinophilic granuloma of bone is another possible manifestation; but in many cases the process causing the lung changes remains obscure. In these various forms of honeycomb lungs progression of the disease is usually extremely slow, and in the early stages the radiographic changes may be present without symptoms and generally are more striking than the symptoms; unless there is severe and prolonged secondary bacterial infection with purulent sputum, clubbing is not observed; spontaneous pneumothorax is frequent; and some of the associated features noted above may be found.

Though lung biopsy may be required to establish a diagnosis of diffuse interstitial fibrosis beyond doubt, in many instances consideration of these points may enable the diagnosis to be sufficiently well based for clinical purposes; and in general it may be said that the need for biopsy varies inversely with the confidence with which the characteristic clinico-radiological picture is recognized.

Prognosis

Both from my own experience of these 26 cases and from published reports it seems that on the whole the acuteness of the disease and the rate at which it progresses tend to vary inversely with age; the older the patient the more likely is it to be only slowly progressive, or even to enter a stationary phase. Fourteen of my patients have received only symptomatic treatment, and, in some cases, antibiotics to control episodes of secondary bacterial infection. The mean age of these patients at the onset of their symptoms was 60 years. Seven of these 14 are dead, and the mean duration of symptoms in them was 4½ years, with a range of 1½ to 7½ years. Seven are still living; the mean duration of symptoms being 5 years, with a range of 1½ to 8½ years. Of those who are still living, four seem to be static under observation; one has recently been in hospital with a severe attack of congestive heart failure due to pulmonary hypertension and right ventricular failure, but has made a good response to treatment; and in two the period of observation has been too brief to permit any estimate of rate of progression. Of the deaths, one was due to bronchial carcinoma which seemed to have developed quite independently, but the other six were due to the interstitial fibrosis; in one of the latter, as mentioned above, histological appearances indistinguishable from those of alveolar-cell carcinoma were present in several parts of the lungs, but no metastases were found. These 14 patients are a selected group, in that they were those in whom under observation the condition did not appear to be progressing very rapidly, and there therefore seemed to be no indication for an attempt to modify the course with corticosteroids.

Trial of Corticosteroids

It is inevitable that in a condition like this the possibility that corticosteroids might delay the progressive deterioration should be considered. A special difficulty, over and above the general difficulties and anxieties entailed by the use of corticosteroids in chronic disease, has been observed in this group of cases. Once one of these patients has been established on a cortico-

steroid withdrawal of the hormone may prove impossible, for even a reduction in dosage may give rise to an acute and possibly uncontrollable exacerbation of symptoms. Three cases of this sort were reported by Peabody, Buechner, and Anderson (1953) in the United States.

Though I have proceeded with considerable caution in the use of corticosteroids in these cases, one of my patients had a mild episode of this sort. This was a woman who was so disabled by dyspnoea that she was unable to move from her bed, so that in spite of the known difficulties I felt justified in seeing whether she could be helped by corticosteroids. We gave her cortisone, starting with small doses and gradually increasing to 100 mg. daily, on which she improved moderately. After three weeks the dose was reduced to 75 mg. daily. Ten days later she became acutely ill with extreme dyspnoea, cyanosis, slight fever, and an increase in the shadowing in the lungs, especially on the right. Fortunately, she recovered from this episode when the dosage of cortisone was increased, and we were later able to reduce the dose very gradually, so that now, three years later, she is still living, though very breathless, taking 10 mg. of prednisolone daily. Because of the danger of such acute exacerbations on reduction of dosage, I think it reasonable, if corticosteroids are used in one of these cases, to start with a small dose and gradually increase it, until either there is a tolerable degree of improvement or it is clear that no improvement will ensue. In the latter event, even more than usual caution in reduction of dosage is required.

It must be remembered that in these patients, once corticosteroid treatment has been started, it is likely to be needed for the rest of the patient's life; and this entails all the hazards of long-term treatment with corticosteroids. To quote an example: a woman aged 56 who had been becoming progressively more breathless for one year because of diffuse interstitial fibrosis of the lungs started corticosteroid treatment in June, 1956, with moderate relief of symptoms. The dose could not be reduced below the equivalent of 50 mg. of cortisone, because such reduction caused desperate dyspnoea. In February, 1958, she complained of backache, and was found to have severe osteoporosis of the spine. In this case we are on the horns of a therapeutic dilemma: the osteoporosis demands the withdrawal of corticosteroids, yet complete withdrawal would undoubtedly lead to death from respiratory insufficiency.

It will be clear from this discussion of the difficulties that corticosteroids should be used in these cases only for certain special indications. In the more chronic form of the disease the possibility of benefit beyond some amelioration of symptoms seems to be slight. If the patient is so disabled that he is incapable of leading any sort of useful life, so that it seems worth while exposing him to a dangerous treatment for the sake of giving him a limited period of more tolerable life, then it is justifiable to face the risks and try the effect of corticosteroids. The more acute type, often seen in younger patients, may be treated with less hesitation, both because their untreated course seems to be more rapidly and uniformly downhill and because, in a few of them, remission both of symptoms and of radiographic changes may occur under treatment and even be maintained, at all events for a time, after gradual withdrawal of the corticosteroids. Such cases have been recorded by others (Harris, Preuss, Goldman, and Friedman, 1957; Read and Holland, 1959), and one of my patients seems to be now in such a remission. But such a favourable response is rare. In the chronic cases with long-standing and only slowly progressive fibrosis, my experience suggests that corticosteroids do not produce any fundamental change in the course of the disease.

Effects of Corticosteroid Treatment

Twelve of my patients have received corticosteroid treatment. In one (Case 3 above), treatment has been withdrawn after 15 months, and she is still free from symptoms and radiographic abnormality five months later, though, as noted below, her diffusing capacity is still abnormal. One experienced limited improvement on corticosteroid treatment, which was withdrawn after 13 months; six months later the radiographic shadowing was still slightly less dense than before treatment, and she claimed to be less dyspnoeic, though there was no improvement in the objective physiological tests of respiratory function. Three showed limited improvement, which is maintained only so long as corticosteroid treatment is continued; to date one has been treated for three years and is now receiving 10 mg. of prednisolone daily, and two have been treated for 18 months and are receiving 10 mg. and 15 mg. of prednisolone daily. In two of these the improvement has been mainly subjective, with slight improvement in physiological tests, but no change in radiographic appearances. The third, a man who was 25 years old at the beginning of his illness, has shown a greater improvement in the physiological tests and some improvement in radiographic appearance, but he has developed a moderately severe Cushing's syndrome.

Two patients have received corticosteroid treatment for three years and one year respectively, and are still surviving with only slight subjective improvement and no physiological or radiographic change; but it is impossible to withdraw the hormone because of increased dyspnoea on reduction of dosage below a critical level. One of these is the patient with osteoporosis of the spine mentioned above. One patient was treated for 16 months in a similar unsatisfactory way, and died out of hospital; no precise information is available about the mode of death. In four patients corticosteroids produced no improvement, and after two or three months were withdrawn without ill effect. Three of these survive $2\frac{1}{2}$, $2\frac{1}{2}$, and $1\frac{1}{2}$ years later, but are slowly deteriorating; and one died with progressive dyspnoea 20 months later.

Some physiological observations are available in 10 of the patients who received corticosteroids. Tests of ventilatory function before and after treatment are available in seven. In three the results were within the normal range before treatment and did not change during corticosteroid treatment; in four, a reduced maximum voluntary ventilation or equivalent measure was increased from a mean of 37 l./min. to 62 l./min. The carbon-monoxide uptake, which correlates best of the normally available tests with disability in cases of this sort, has shown only moderate improvement while the patients are receiving corticosteroids. In six patients in whom results before and during treatment are available, the mean figure for carbon-monoxide diffusing capacity at rest by the steady state method was 8 ml./min./mm. Hg before and 10 ml./min./mm. Hg during treatment. In four in whom results are available also

after cessation of treatment the mean figures are 8 before, 12.9 during, and 6.5 after treatment. These figures fit well with the clinical impression that, while an exceptional case treated early in the disease may show a more favourable response, all that can be expected of corticosteroid treatment is that it may suppress the progress of the disease process and certain of its symptoms, and that the favourable effects, if any, do not usually continue after cessation of treatment.

Successful treatment of these cases will probably have to await more complete knowledge of their aetiology. At present, in our study we are in the preliminary stage of collecting information and building up an accurate description of every aspect of them. To go back to a point mentioned earlier, I think that at the moment it may be obscuring important issues to call the whole of this group the Hamman–Rich disease or Hamman–Rich syndrome. If those words mean anything, they would imply that the chronic cases represented a chronic reaction to the same noxious process, whatever it may be, to which the original cases described by Hamman and Rich were an acute reaction. This may or may not be found eventually to be true; but in our present state of ignorance the use of a form of words which assumes tacitly that it is true implies the uncritical acceptance of so many unproved hypotheses that it only confuses our thought, and this should certainly be avoided. For this reason I prefer to refer to this fascinating group of cases in the chronic stage by the purely descriptive name, chronic diffuse interstitial fibrosis of the lung of undetermined aetiology.

Summary

Twenty-six cases of chronic diffuse interstitial fibrosis of the lungs have been observed during a period of nine years. Their clinical, radiological, and physiological features are described, and an account of the morbid histology, based upon studies in 13 of them, is given. The prognosis is discussed, and the effects of corticosteroid treatment in 12 cases are described.

In this lecture, which was intended to recount my own experience, I have not attempted a formal review of the extensive literature. Good reviews have been published by Grant, Hillis, and Davidson (1956) and by Rubin and Lubliner (1957). I have previously published a brief account of 12 of my cases (Scadding, 1956).

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RESPIRATORY SYMPTOMS, BRONCHITIS, AND VENTILATORY CAPACITY IN MEN

AN ANGLO-DANISH COMPARISON, WITH SPECIAL REFERENCE TO DIFFERENCES IN SMOKING HABITS

BY

H. C. OLSEN, M.D.

Rønne, Bornholm

AND

J. C. GILSON, M.B., F.R.C.P.

Director, Medical Research Council Pneumoconiosis Research Unit, Llandough

Reid (1956) has drawn attention to the striking difference in the crude mortality rates (per million) from bronchitis in Great Britain (838) and in Denmark (33). Christensen and Wood (1958) concluded that these differences were most unlikely to be caused solely by diagnostic differences in the two countries. They suggested that, as the cigarette consumption in England and Wales was about double that in Denmark, this might be an important factor causing the difference.

Dr. A. L. Cochrane suggested that Bornholm might be a suitable place to make a direct comparison with the surveys made in South Wales and Scotland of respiratory symptoms (Higgins, 1957; Higgins and Cochran, 1958) because the island has been the centre of a number of successful epidemiological studies (Olsen, 1943; Fremming, 1951; Dencker and Felbo, 1958). In South Wales (Vale of Glamorgan) and in Scotland (Annandale) the populations were defined by private census, and a random sample of men aged 55–64 were asked to collaborate. In Bornholm one of us (H. C. O.) has for a number of years called up age-defined groups for examination as part of the programme for the control of tuberculosis, using the civil population lists. The response has been excellent, and it seemed probable that if men aged 55–64 were sampled from the town list of Rønne (where the principal tuberculosis dispensary in the island is situated) we might expect a response as good as that achieved by Dr. Higgins (over 90%).

Bornholm is an island of about 588 square km. situated in the Baltic, 200 km. off the east coast of Zeeland, the largest Danish isle. It forms one of the administrative counties of Denmark and has a population of 48,959. About half the population live in the country and the remainder in the few small towns, the largest of which is Rønne, on the west coast.

Most of the population are directly or indirectly employed in agriculture or fishing, but there is an important granite industry, and a large factory making fire-bricks, glazed tiles, and drain-pipes.

Rønne has a population of 13,200; it is the commercial centre of the island and a fishing port. It is a strikingly clean and well-kept town and has no slums or visible atmospheric pollution. The average temperature in February is 32.2° F. (0.1° C.), and in July 61.4° F. (16.3° C.). This is only a little colder in winter and a little warmer in summer than the Vale of Glamorgan and Annandale. At the turn of the

seasons, in spring and autumn, there is a period when the island is frequently enveloped in cold but clean sea-fogs. The rainfall (0.5 m. per annum) is about half that in the Vale of Glamorgan and Annandale. The population density in Rønne is about 14 persons per hectare (35 per acre), but this is an underestimate of the true figures, since most of the people live within an area which is only about one-third the total within the town boundary. The population density in the Vale of Glamorgan is 0.5 per acre and in Annandale 0.1 per acre.

Procedure

The town list is kept up to date every three months, and all those residing there for three months or more must register their age, occupation, and address with the civil authorities. There is also an annual list of tax assessments of all residents which provides an index of economic status because the assessment is proportional to total income from all sources.

A list of all men aged 55–64 on April 1, 1958, was prepared from the register, and a sample of 200 chosen at random from this list. During May, 1958, the practitioners were notified of the survey, and the local press gave accounts of the intended investigation and asked for the collaboration of those who were chosen to attend. The selected men were written to a few days ahead and were asked to attend at the dispensary in the late afternoon or evening on a given day. Those who failed to attend received a personal letter by the first post the following morning, and were also contacted by telephone in many instances. The survey lasted three weeks from the beginning of June, and took place in fine weather. The two surveys in the U.K. also took place in the spring and summer.

Methods

The respiratory symptoms, past medical history, and smoking habits were recorded by one of us (H.C.O.) using essentially the same standardized questionary which was used by Higgins (1957) and Higgins and Cochran (1958) and which has been studied for reproducibility by Fairbairn, Wood, and Fletcher (1959) and Higgins, Cochrane, Gilson, and Wood (1959) and shown to give reasonably consistent assessments of many of the symptoms. It was identical with the one now in use in the study of bronchitis by the College of General Practitioners in the U.K. The principle in its design is the recording of the main respiratory symptoms in response to standard questions—the wording of which has been modified by trial and error to remove ambiguities so far as is possible. The pattern of symptoms at different ages and in different groups can then be compared without reaching a final definition of chronic bronchitis, about which there is at present no general agreement.

Nearly all the men called up had already attended the dispensary on at least one occasion in the past, and complete records of tuberculin sensitivity and the results of *x*-ray examinations were available. In those in whom this information was lacking, a Mantoux test was made (10 units P.P.D.). Screening of the chest was done on all subjects by H.C.O., and films were obtained where there was any doubt about the observations.

Four physiological measurements were made by J.C.G. (1) The forced expiratory volume (F.E.V.) over 0.75 second following a maximal inspiration. This volume was multiplied by 40 to give a measure of the breathing capacity (I.M.B.C.) (see Gandevia and Hugh-Jones, 1957, for terminology). The mean of three measurements (after rejection of the first two trials) was accepted and the volume corrected to B.T.P.S. (2) The forced vital capacity (F.V.C.). (3) The percentage change in nitrogen between 750 and 1,250 ml. on the alveolar plateau following a single breath of oxygen using the Lilly type of nitrogen meter (Comroe and Fowler, 1951). The method of calculation was simplified by making the pen recorder write on a drum mounted on the wheel of a spirometer. In this way a direct plot of nitrogen percentage against volume was obtained. The time marker was used to check that the expiratory flow rate was not excessive. The mean of three measurements was adopted. The test provides an index of the uniformity of ventilation within the lungs. (4) The peak flow during a maximal forced expiration was estimated, using the Vane type of recorder developed by Wright and McKerrow (1959). Special calibration checks on the instruments were made, so as to ascertain that no instrumental bias could account for differences obtained in this survey and those made by Higgins.

Weight (to the nearest 0.1 kg.) and height and stem height (to the nearest 0.5 cm.) were measured by Miss S. Hansen, who also acted as interpreter during the physiological tests.

The Sample

TABLE I.—*Sample of Men Aged 55–64 Living in Rønne*

Total Population April, 1958	Males Aged 55–64	No. in Sample	No. Attending	Too Ill or Away	Refused
13,200	594	200	183* (91·5%)	3	14

* 3 men left between April 1 and June 1 and were replaced by substitutes chosen at random.

TABLE II.—*Relation of Anthropometric and Physiological Measurements, and Tax Assessments to Willingness to Attend*

	No.	%	Age	Weight (kg.)	Sitting Height (cm.)	I.M.B.C. (l./min.)	Peak Flow (l./min.)	Tax Index Median
Group 1	139	69·5	58·6	80·7	87·4	107	474	1,060
,, 2	25	12·5	58·9	80·8	86·7	110	505	783
,, 3	19	9·5	58·6	82·3	86·7	104	461	750
Refused	14	7·0	—	—	—	—	—	450
Too ill or away	3	1·5	—	—	—	—	—	—

For definition of groups see text.

Table I shows that 91.5% of the men selected at random were examined. This is practically the same response rate as obtained by Higgins in his survey. In Table II the 183 men are divided into three groups according to their willingness to attend. Group 1—those who came in response to a first letter; group 2—those who came after a second letter and/or telephone call; and group 3—those who came only after more persuasion, including in some cases home visits. There is no trend relating weight or height or physiological results to willingness to attend, but there is to the index of tax assessment; those who refused paid on the average less in taxation than those who attended. The high proportion of men in group 1 is impressive evidence of the interest shown in the survey. We conclude that the sample examined was probably representative of the whole, and can with reasonable confidence be compared with the samples seen by Higgins. Out of the 183 who attended, 160 had been examined previously at the dispensary as part of the tuberculosis control in

the island. 23 men attended for the first time. Of the lapses, six had previously been seen at the dispensary.

Prevalence of Respiratory Symptoms

In both areas studied by Higgins there were a few men with mining and quarrying experience. These men were found to have more symptoms and a lower ventilatory capacity, and so were omitted in his strict comparison of agricultural workers between the two areas. To make our comparison as strict as possible we have done the same and removed 27 men who had worked one or more years in quarries. Table III shows for

TABLE III.—*Prevalence of Respiratory Symptoms in Random Sample of Men Aged 55–64 in Bornholm, Wales, and Scotland*

Symptom	Annandale	Vale of Glamorgan	Rønne	Significance
No. in sample ..	87	86	156	
Cough	25 (28·7)	27 (31·4)	27 (17·3)	<0·05
Sputum	20 (23·0)	24 (27·9)	17 (10·8)	<0·01
Cough and sputum ..	17 (19·5)	22 (25·6)	14 (9·0)	<0·01
Wheeze	38 (43·7)	41 (47·7)	24 (15·4)	<0·01
Haemoptysis ..	5 (5·7)	7 (8·1)	0 (0)	<0·01
Weather affecting chest	9 (10·3)	10 (11·6)	15 (9·6)	N.S.
Chest illness in previous 3 years with cough and sputum	16 (18·3)	14 (16·3)	10 (6·4)	<0·01
1	12 (13·8)	10 (11·6)	10 (6·4)	N.S.
2 and more ..	4 (4·6)	4 (4·7)	0 (0)	
Past illness:				
Pneumonia ..	21 (24·1)	16 (18·3)	30 (19·2)	N.S.
Pleurisy	7 (8·0)	9 (10·5)	10 (6·4)	,,
Bronchitis ..	13 (14·9)	20 (23·3)	26 (16·7)	,,
Asthma	5 (5·7)	5 (5·8)	3 (1·9)	,,
"Chronic bronchitis"	6 (6·9)	5 (5·8)	4 (2·6)	,,

The questionaries and tables of symptoms in detail can be obtained from the Pneumoconiosis Research Unit. "Chronic bronchitis" is defined as those with persistent sputum and at least one chest illness in the previous three years. The significance test in each case was a χ^2 with 2 degrees of freedom. Percentages are shown in parentheses.

the three surveys the absolute numbers and percentage prevalence of those symptoms which are most reproducibly assessed. The striking similarity of prevalence in Annandale and the Vale of Glamorgan has already been commented on by Higgins and Cochran (1958). We now see the prevalence is much lower among the men in Rønne, about half or less. A feature is the absence in Rønne of any men with more than one chest illness with increased cough and sputum in the previous three years. The proportion reporting that the weather affected their chest is similar in all areas.

It is also of interest that the percentage reporting attacks of pneumonia, pleurisy, or bronchitis in their past history is also similar in all areas. Asthma was reported less often in Rønne, but the difference is not statistically significant. The proportion with "chronic bronchitis," when arbitrarily defined as those with persistent sputum and a chest illness in the previous three years, is very similar in Annandale and the Vale of Glamorgan, but only about half as frequent in Rønne. However, the number of cases is small and the difference not statistically significant. The significant differences in the prevalence of the common symptoms between Rønne and the two U.K. samples could be due to a large bias in the recording between the two observers concerned. We have no direct evidence on this point, which must inevitably be in doubt to some extent in such international comparisons on account of the language difficulties. The similarity of the prevalence of past illnesses in all three areas makes it seem unlikely that there is a big bias in recording, and the findings confirm the impression one of us got during the survey of the small proportion who coughed or produced any wheezing during the physiological measurements.

Table IV summarizes the clinical grading of the degree of breathlessness using a scheme based on that suggested by Fletcher (1952). Grade 2 and over are all those who replied "yes" to the question, "Do you have to walk slower than other people of your own age on the level because of breathlessness?" Grade 3 are those who replied "yes" to the question, "Do you ever have to stop for breath when walking at your own pace on the level?"

The proportion in the two groups is similar in the U.K. samples, and again about one-half in Rønne, but the differences are nearly statistically significant ($P=0.062$).

Fletcher *et al.* (1959) have recently published the prevalence of respiratory symptoms of a sample of London Post Office workers using the same questionary. Table XII (in the Appendix) shows a comparison of the men in London aged 50–59 and those in Rønne aged 55–64. There is a much higher prevalence of symptoms in the Post Office workers, especially in the more severe symptoms such as "persistent cough and sputum throughout the day," and also in the frequency of chest illnesses.

Anthropometry

Table IV shows that there is little difference in average height between men in Rønne and Annandale, but the men in the South Wales sample are 4 cm. (1.58 in.) shorter. The sitting height, which is more closely related to lung function than total height, was only about 1 cm. less in the men in Rønne than in the two other groups. The differences in stem height between the groups are too small to have affected materially the physiological findings. The men in Rønne were on the average 10 kg. (22 lb.) heavier than men in the other two areas.

Ventilatory Capacity

The I.M.B.C. was on the average 11 l./min. (12%) higher in Rønne than in Annandale, and 17 l./min. (19%) higher than in the Vale of Glamorgan. The difference between Rønne and the other two areas is statistically significant at the 0.001 level.

The differences between Rønne and the other two samples cannot be accounted for by differences in the size or weight of the men. Studies of observer bias in recording the F.E.V. between Higgins and J.C.G.

TABLE IV.—*Anthropometry, Ventilatory Capacity, and Clinical Grades of Dyspnoea in Samples of Men Aged 55–64 in the Three Areas (Excluding Miners and Quarrymen) (Means)*

Area	No. in Sample	Height (cm.)	Sitting Height (cm.)	Weight (kg.)	I.M.B.C. (l./min.)	Peak Flow (l./min.)	N_2% Change	Clinical Grade	
								2 and Above	3 and Above
Rønne	156	171·0	87·2	80·4	106·3*	470†	1·66	25 (16%)	7 (4·5%)
Annandale	87	170·9	88·6	72·1	95·1	441	—	25 (28·7%)	8 (9·2%)
Vale of Glamorgan ..	86	166·9	88·1	69·1	89·1	494	—	21 (24·4%)	7 (7·9%)

* Difference between Rønne and Annandale or Vale of Glamorgan is significant at 0·001 level. Annandale and Vale not significantly different.
† Difference between Annandale and Vale of Glamorgan is significant at 0·02 level. Rønne not significantly different from either.

(Higgins *et al.*, 1959) have failed to demonstrate statistically significant differences, and it is unlikely that out of the 17-l. difference more than 3 l. could have arisen on account of differences in the observers.

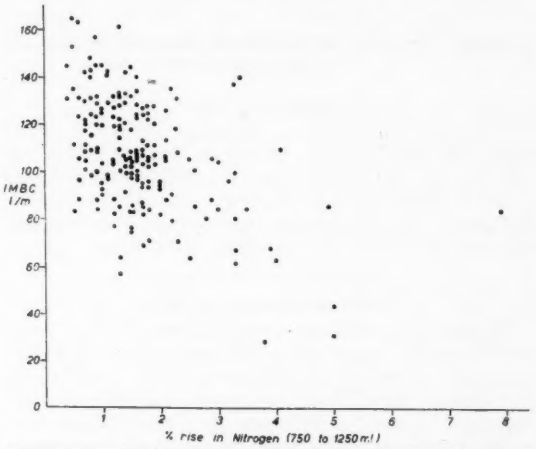
The peak flow (l./min.) usually correlates highly with the I.M.B.C. (r=approximately 0.8; Wright and McKerrow, 1959), so we might have expected this test to assess the areas in the same order as the M.B.C. Table IV shows that this is not so: the men in Rønne lie between those in Scotland and South Wales, and the latter two are reversed in order as compared with the M.B.C. The cause of this is unlikely to be instrumental. Nor is it likely to be due to a larger random error in recording the peak flow, because the ratio of instrumental and subject errors (standard error of the mean of three readings on a subject to the standard deviation of the mean within the population) is similar for peak flow and F.E.V. But Fletcher (personal communication) has shown that different observers do get significantly different values with the peak-flow meter. The reading depends more on the force (and hence co-operation) put into the effort of blowing than is the case with the F.E.V. (McDermott and McKerrow, 1956). We think the apparently anomalous results are likely to be due to small differences in the co-operation achieved when doing the test, and this could produce a bias between one group and another.

TABLE V.—*Frequency Distribution of I.M.B.C. and F.E.V. in Men Aged 55–64 in Rønne and Annandale (Excluding Quarry Workers)*

I.M.B.C. (l./min.)	F.E.V.$_{0\cdot75}$ (l.)	Rønne		Annandale	
		No.	%	No.	%
10–	0·25	—	—	1	1·1
20–	0·5	1	0·6	—	—
30–	0·75	1	0·6	3	3·5
40–	1·0	1	0·6	1	1·1
50–	1·25	2	1·2	2	2·3
60–	1·5	7	4·5	6	6·9
70–	1·75	4	2·6	12	13·8
80–	2·0	22	14·1	5	5·7
90–	2·25	21	13·5	16	18·4
100–	2·5	32	20·5	15	17·2
110–	2·75	14	9·0	11	12·6
120–	3·0	23	14·7	10	11·5
130–	3·25	14	9·0	2	2·3
140–	3·5	9	5·8	1	1·1
150–	3·75	2	1·2	1	1·1
160–	4·0	3	1·9	1	1·1
	Total ..	156	99·8	87	99·9

Table V shows the frequency distribution of I.M.B.C. (and F.E.V.$_{0\cdot75}$) in Rønne and Annandale, excluding quarry workers. It shows that only 2% of men had a value less than 50 l./min. in Rønne, compared with 6% in the Annandale sample, which is the most "healthy" population sample yet reported in U.K.

The nitrogen meter was not used in the surveys in the Vale of Glamorgan and in Annandale, and so no comparisons are available for the distribution of the rise in percentage of nitrogen on the alveolar plateau, shown for Rønne in Table VI. The distribution is skew; in fact, close to log normal. The mean is 1.7%, and a quarter of the subjects have a N_2% less than 1, whereas only 15% exceed 2.5 N_2%; 6.5% have a change of nitrogen of 3.5% and above. Below is shown a scatter diagram relating the I.M.B.C. to the change in nitrogen percentage. The three men who had an I.M.B.C.



Scattergram showing relation of indirect maximum breathing capacity and nitrogen clearance from lung after a single breath of oxygen.

of 50 l. and below have a change of nitrogen exceeding 3.5%, but there are 10 men who had a change of nitrogen percentage of 3.5 or more who had comparatively high values of M.B.C. though only one of them was above the mean. By using the M.B.C. only, we are clearly missing some people who may be considered to have a ventilatory defect in the sense that they show evidence of marked inequality of ventilation.

TABLE VI.—*Frequency Distribution of Nitrogen Rise in the Alveolar Plateau in Men Aged 55–64 in Rønne (Excluding Quarry Workers)*

N_2%	No.	%	N_2%	No.	%
0·0–	2	1·3	4·5–	1	0·6
0·5–	37	23·7	5·0–	2	1·3
1·0–	37	23·7	5·5–	0	—
1·5–	43	27·6	6·0–	0	—
2·0–	14	9·0	6·5–	0	—
2·5–	7	4·5	7·0–	0	—
3·0–	6	3·9	7·5–	1	0·6
3·5–	4	2·6			
4·0–	2	1·3	Total	156	100·0

Men with Quarrying Experience

For the reasons given we omitted the men with quarrying experience in Rønne when making the strict comparisons with the U.K. sample, but Table VII shows that in Rønne these quarrymen did not differ strikingly from the remainder of the sample in respect of ventilatory capacity or anthropometry. Their M.B.C. at 112 l./min. was slightly higher than the average for the whole group. The percentage prevalence of sputum, cough and sputum, and wheeze was higher than in the remainder of the group, but there are too few men in

TABLE VII.—*Anthropometry, Ventilatory Capacity, and Respiratory Symptoms of the 27* Men Aged 55–64 Doing One or More Years' Quarrying Work in Rønne*

Height (cm.)	Sitting Height (cm.)	Weight (kg.)	I.M.B.C. (l./min.)	P.F. (l./min.)	N_2%	Tax
172	87·5	84	112	518	1·63	845

	Cough	Sputum	Cough and Sputum	Wheeze	Weather Affecting Chest	Total Chest Illnesses Last 3 Yrs.	Chronic Bronchitis
No.	6	7	6	6	3	2	1
%	22	26	22	22	11	7	3·5

* Including two men with pneumoconiosis category 1.

the group for any firm conclusions to be drawn about the prevalence of symptoms.

We think, therefore, we have demonstrated that there is a lower prevalence of respiratory symptoms and a higher average ventilatory capacity in men in Rønne than in those living in the agricultural areas of the Vale of Glamorgan and in Annandale. What is the explanation of this difference ?

Possible Causes for the Difference between Danish and U.K. Samples

Atmospheric Pollution

Atmospheric pollution is strikingly absent from all areas and the climatic differences are not large. It seems most improbable that the differences observed could be directly related to general air pollution. Also, the proportion of subjects reporting that the weather affected their chest was the same in all areas.

Social and Economic Factors

Higgins and Cochran (1958) observed that when comparing the urban and rural communities the higher prevalence of symptoms might have been associated with the higher population density in the urban area. However, as this density in Rønne is much higher than in the two agricultural areas in the U.K., population density cannot explain the differences. The men in Rønne are much heavier than those in the other two areas, but as they are about the same height it seems reasonable to conclude that they probably eat more. They now have a diet which is probably rich in carbohydrate and fat (butter). We do not know how such a dietary difference (if it exists) could beneficially affect their chests to the extent observed. The men in Rønne have undoubtedly enjoyed a high standard of living over many years, and this may in some ill-defined way benefit their chests. It is possible that the relative isolation of the island has protected them to some extent from epidemics of upper respiratory infection, but as there is a daily boat to and from the mainland the isolation is by no means complete.

Smoking

Higgins (1959) studied the effect of smoking on respiratory symptoms and ventilatory capacity in five random samples of men of this age-group. He found a striking difference between the smokers and non-smokers, and also a trend of increasing symptoms and reduced ventilatory capacity within those who smoke. Table VIII compares the smoking pattern of the men in Rønne and in the five samples from the U.K. The percentage of non-smokers in Rønne (15.9) is double that in the U.K. The proportion of ex-smokers is the same in all samples. The Table also shows that among those who smoke there is a tendency to smoke less in Rønne than in the U.K. In Rønne 64.1% of the smokers smoked less than 15 g. a day, whereas in the U.K. samples this figure was 55.9%.

In the U.K. sample the majority of smokers (82%) smoked cigarettes alone or combined with pipes. Only about 20% smoked pipes alone. The situation is very different in Bornholm, where, out of the 128 smokers, only 40 (31%) smoked cigarettes at all; 14.1% were purely cigarette smokers; 15.7% smoked pipes only; and 25.8% cigars alone.

The relatively high proportion of pure cigarette, cigar, and pipe smokers enables a comparison of the effects of taking tobacco in these three ways to be made. Table IX shows this comparison for men smoking 5 g. and more tobacco a day. The average M.B.C. of the 13 purely cigarette smokers was 91 l./min., compared with 113 for the pipe smokers and 117 for the cigar smokers. The difference of over 25 l./min. between the cigarette smokers and the cigar smokers is statistically significant ($0.05>P>0.02$), as is the difference between the cigarette smokers and the pipe smokers ($0.02>P>0.01$). The average I.M.B.C. of the cigarette smokers differs significantly ($P>0.01$) from the other three groups (mean 110.8 l./min.), which do not differ significantly from each other. It will be seen that the average for the cigar and pipe smokers is in fact above that of the non-smokers.

TABLE IX.—*Comparison of Non-smokers and Those Who Smoke Only Cigars, Pipes, or Cigarettes (5 g. and Over of Tobacco Per Day)*

	No.	I.M.B.C. (l./min.)	Peak Flow (l./min.)	N_2%	Tax Index	$\frac{F.E.V._{0.75} \times 100}{F.V.C.}$	Average Weight Smoked (g./Day)
Non-smokers	29	106·2	476	1·57	790*	70·0	—
Cigars only	18	116·6	500	1·44	2,340	73·0	14·9
Pipes only . .	15	112·6	453	1·49	872	69·3	12·9
Cigarettes only . .	13	91·1	420	2·65	1,810	67·0	12·1

* Based on 26.

I.M.B.C.: Cigar *v.* cigarette, $0.05>P>0.02$ (other differences N.S.). Pipe *v.* cigarette, $0.02>P>0.01$.
Peak flow: N.S.
Nitrogen % (using log N_2): Cigar *v.* cigarette, $0.05>P>0.02$.
$F.E.V._{0.75}/F.V.C.$ %: N.S.

The mean nitrogen percentage change is 2.65 for the cigarette smokers, and 1.44 and 1.49 respectively for the cigar and pipe smokers. The difference between the cigar and cigarette smokers is significant when using a log scale (in view of its skew distribution) for calculation of the nitrogen percentage.

The average tax paid by the cigarette smokers and cigar smokers was not very different, whereas the pipe smokers and the non-smokers paid only about half as much. The average weight of tobacco smoked was 14.9 g. a day for the cigar smokers and 12.1 for the cigarette smokers. The average values for the peak flow and the F.E.V. %/F.V.C. show a similar trend

TABLE VIII.—*Smoking Pattern (g./day) of Men Aged 55–64 in Rønne (Quarrymen Included) and in Five Random Samples in U.K.*

	Total Sample	Smokers						Ex-smokers	Non-smokers
		No.	1–4 g.	5–14 g.	15–24 g.	25–49 g.	50+ g.		
Rønne	183	128 (69·9)	29 (22·6)	53 (41·4)	35 (27·3)	11 (8·6)	1 (0·1)	26 (14·2)	29 (15·9)
U.K.	971	773 (79·6)	43 (5·6)	389 (50·3)	251 (32·5)	89 (11·5)		126 (13·0)	72 (7·4)

Percentages are shown in parentheses.

between the cigar and cigarette smokers, with the pipe smokers intermediate, but the differences are not statistically significant. It is interesting that the non-smokers have a lower average I.M.B.C. than the cigar smokers. This may be partly socio-economic in view of the lower average tax index, though there is no clear relation between the I.M.B.C. and the tax index in the whole group.

Non-smokers

In view of the relation between smoking and ventilatory capacity we have in Table X compared non-smokers in the two U.K. samples and in Bornholm, both for respiratory symptoms and M.B.C., using only men who have not worked in the quarries or mines. The numbers are very small in such "pure" groups. The average M.B.C. in Rønne and the two U.K. samples together, is the same (108 l./min.). None of the 11 men in the U.K. samples had respiratory symptoms, chest illnesses, or complaint of breathlessness. In the 24 men in Rønne the prevalence of symptoms is less than in the whole sample (Table III), but higher than in the U.K. samples. This is the only comparison where the general trend of differences between Rønne and the U.K. disappears or reverses, and perhaps suggests that the differences between Rønne and the U.K. are largely the result of differences in smoking habits.

TABLE X.—*Non-smokers. Excluding Quarryworkers and Miners*

Sample	No.	I.M.B.C. (l./min.)	Cough	Sputum	Wheeze	Chest Illnesses		Grade 2+
						1	2+	
Rønne	24	108	2 (8%)	2 (8%)	2 (8%)	4 (16%)*	0	4 (16%)
2 U.K.	11	108	0	0	0	0	0	0

* Two chest illnesses were pneumonia and hypertensive heart failure.

Examination for Tuberculosis

Table XI shows the results of the study of tuberculin sensitivity. 78% of the sample seen were naturally Mantoux-positive, and a further 10% were positive as a result of previous B.C.G. vaccination. Eight of the men who were negative were vaccinated with B.C.G. in accordance with the policy pursued in Bornholm (Olsen, 1943).

TABLE XI.—*Mantoux Tests*

	Negative	Natural Positive	B.C.G. Positive	Total	Not Examined
No. . .	22 (12%)	143 (78%)	18 (10%)	183	17

No clinically significant cases of tuberculosis were revealed during *x*-ray screening. Two cases of category 1 silicosis which were already known were included among 27 quarrymen whose names appeared in the sample.

Discussion

Our comparative study of representative samples of the population of males aged 55–64 in Rønne and in two agricultural areas in the U.K. has demonstrated a lower prevalence of respiratory symptoms (but not of past chest illness) in Rønne. The higher average I.M.B.C. in Rønne supports the conclusion that there is a real difference in the prevalence of non-specific chronic chest disease in the two countries. Differences in height, weight, and population density cannot account for the findings, while atmospheric pollution is minimal in all three areas.

Tobacco smoking is, however, a possible explanation; there are more non-smokers in Rønne, and those who smoke tend to smoke less than in the U.K., with a striking difference in the proportion of men smoking cigarettes—over 80% in the U.K., only about 30% in Rønne in this age-group. Looked at in another way, men of this age in Rønne smoke only 780 cigarettes per head per annum compared with 3,400 smoked in the U.K.

The percentage of non-smokers (15%) observed in Rønne is rather lower than the 25% reported for men of the same age in the Danish National Morbidity Survey of 1950 (Hamtoft and Lindhardt, 1955), and is possibly attributable to our stricter definition of non-smokers. The relatively small proportion of cigarette smokers compared with pipe and cigar smokers we found is in accord with their findings.

A feature of the group seen in Rønne is that no man had more than a single chest illness with increased sputum in the previous three years; thus recurrent bronchitis, which is so common in some of the other groups studied in the U.K., was absent. In the period 1951–6 inclusive only 16 deaths from bronchitis were recorded in Bornholm for all ages in both sexes—a crude death rate of 4.8 per 100,000 per annum, which is in line with the general figure for Denmark.

Two of the physiological tests, the I.M.B.C. and the nitrogen curve following a breath of oxygen, indicate that those who smoke only cigarettes have more impairment of lung function than those who smoke only cigars, despite both groups smoking a similar weight of tobacco per week, and having a similar economic status as judged by their annual tax assessment. The number of subjects in these "pure" groups of two types of smoking is small, and the comparison should, we think, be made in larger samples and in other countries where there are enough cigar and cigarette smokers.

Franklin (1958) has reported that smokers show impairment of the mechanics of breathing compared with non-smokers. Eich *et al.* (1957) and Attinger *et al.* (1958) reported that a single cigarette increased the pulmonary airway's resistance in subjects with chronic obstructive emphysema but not in normal subjects. Our results suggest that it would be worth while to extend such studies to the acute effects of cigars and pipes. It may be that there are important differences in the pharmacological action on the lung of different kinds of smoking. Cigar smoke is reported to be alkaline, whereas that from cigarettes is usually acid (Cook, 1957).

The severity of the bronchial irritation may be a factor of importance in the aetiology of lung cancer (Burnet, 1958). Case and Lea (1955) showed that a history of bronchitis is related to subsequent development of lung cancer. Doll and Hill (1956) and Hammond and Horn (1958) found that the risk of lung cancer is higher in cigarette smokers than in pipe or cigar smokers. In our survey the tests of lung function place the types of smoking in the same order. The cigarette smokers were most affected, the cigar smokers least, with the pipe smokers intermediate. These tests of ventilatory capacity and gas distribution are likely

to be a rough measure of the severity of bronchial irritation because they are influenced by inflammation, oedema, and secretions in the bronchial tree. If the risk of developing lung cancer is determined both by the severity of the chronic bronchial irritation and by the presence of carcinogens in the smoke, Wynder's (1959) finding of similar carcinogenic activity in the tars of cigarette, pipe, and cigar combustion is understandable. We would expect the severity of the bronchial irritation to be dependent on many factors, such as the way the tobacco is smoked and characteristics of the smoke not closely related to the carcinogenic activity of the tars.

A better understanding of the factors influencing the severity of bronchial irritation produced by different types of smoking and different tobaccos would be of help in the prevention of bronchitis and perhaps lung cancer in those who smoke.

Reid (1958) has emphasized the relation of atmospheric pollution to bronchitis. Higgins *et al.* (1956, 1959) have shown the importance of mining and smoking as a cause of increased respiratory symptoms and reduced ventilatory capacity. Thus the very low prevalence of non-specific chronic respiratory disease in Rønne is likely to be the result of a number of favourable factors operating together.

This international epidemiological comparison has shown the need to standardize for both the amount smoked and the type of smoking when studying chronic non-specific respiratory disease, and indeed when attempting to define normal lung function. It has also demonstrated the practicability, in favourable circumstances, of such international epidemiological studies without the use of a large team of investigators.

Summary

Representative samples of men aged 55–64 in Rønne (Bornholm) and two agricultural areas in the U.K. are compared for prevalence of respiratory symptoms and ventilatory capacity.

The prevalence of symptoms is significantly lower in Rønne. The mean indirect maximum breathing capacity (I.M.B.C.) is significantly higher in Rønne (106 l./min.) than in the U.K. samples (92 l./min.). The differences are not explicable on the basis of differences in height, weight, density of population, or atmospheric pollution.

There are more non-smokers in Rønne and many fewer cigarette smokers than in the U.K. samples. Only in the small group of non-smokers are there no physiological or clinical differences between Rønne and the U.K. sample. In Rønne there was a significantly lower I.M.B.C. and poorer single-breath nitrogen clearance in the pure cigarette smokers than in the cigar smokers—despite similar tobacco consumptions.

The results are discussed in relation to the problem of bronchitis and lung cancer. The practicability of international comparisons of this type, using standardized criteria and tests, are demonstrated.

We thank Miss S. Hansen for her part in the survey; Mr. B. A. Cross and Mr. P. D. Oldham for the statistical analysis; and Dr. V. Timbrell and Mrs. M. McDermott for designing and making the nitrogen meter. We are grateful to our colleagues for much helpful criticism during the preparation of this paper.

APPENDIX

TABLE XII.—% *Frequency of Symptoms in Total Rønne Sample Compared With Those of Post Office Workers in London*

Question	Rønne Aged 55–64	Post Office Workers Aged 50–59
1: Cough, usually	18	37
2: Cough on rising, winter	16	54
3: ,, ,, summer	2	39
2+4: Cough all day, winter	1	20
2+5: ,, ,, summer	0	11·5
6: Phlegm usually	13	47
7: ,, on rising, winter	10	47
8: ,, ,, summer	1	32
7+9: Phlegm all day, winter	1	25
7+10: ,, ,, summer	0	13·5
*17: Dyspnoea grade 1 (no dyspnoea)	73	64
,, ,, 2	11	20
,, ,, 3	15	14
,, grades 4 and 5	0·5	2
22: Wheeze occasionally	16	50
23: ,, most days or nights	0·5	20
29: Colds usually go to chest	15	37
31: Chest affected by weather	10	41
43+43a: Chest illnesses: †only 1	7	15
,, ,, †2 or more	0	25

* The wording of the questions was not identical in the two surveys. This may in part account for differences in proportion in each grade.
† Excluding illnesses stated to be less than 1 week in duration.

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There are still many patients who die of cancer without ever being in hospital, according to the 1958 Annual Report of the South Western Regional Cancer Records Bureau (Director, Mr. R. M. Vick). In 1958 the number of such patients recorded in the Bureau's area was 1,786. The Report also states that the Bureau was asked to find out how many cases of leukaemia occurred among patients who had throughout the years been treated for cancer of the cervix; in 2,250 such cases only 1 case of leukaemia was recorded.

SIMPLIFICATION OF HALDANE'S APPARATUS FOR MEASURING CO_2 CONCENTRATION IN RESPIRED GASES IN CLINICAL PRACTICE

BY

E. J. M. CAMPBELL, M.D., Ph.D., B.Sc., M.R.C.P.
Medical Unit, Middlesex Hospital, London

There is a need for a method of measuring the CO_2 concentration in respired gases which is more accurate than the many simple clinical analysers but which is less complicated than the Haldane and Scholander methods. The ideal instrument for use in the rebreathing method (Campbell and Howell, 1960) should have an accuracy of ± 0.05–0.1% together with the following properties: portability, simplicity, speed, ease of servicing, and cheapness. The classical Haldane apparatus was simplified until the present instrument (see Diagram) was obtained; it is similar in principle

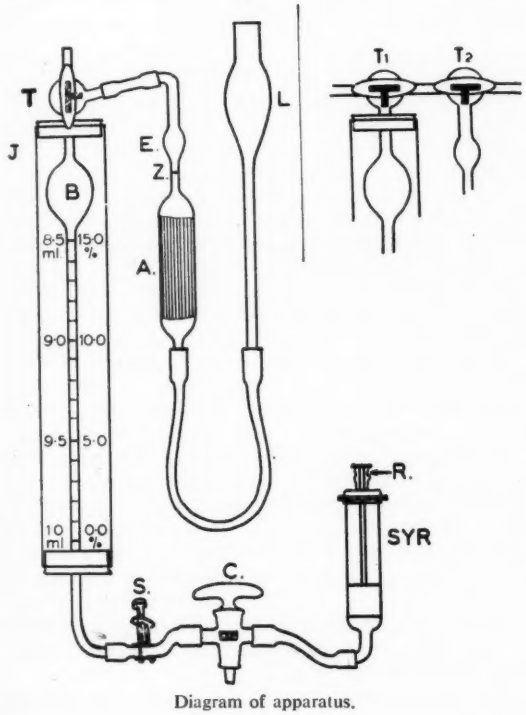

Diagram of apparatus.

to the portable apparatus for determining small percentages of CO_2 described by Haldane and Graham (1935). The chief differences from the standard Haldane apparatus are: absence of O_2 absorption pipette; absence of a compensating burette; replacement of the twin-bore tap on the calibrated burette (B) by a three-way tap (T) (this modification simplifies the setting of the liquid level in the absorption pipette (A) to read zero (Z) at atmospheric pressure); replacement of the mercury-levelling bulb with a syringe (SYR).

Other minor alterations include: the use of a cock (C) between the syringe and burette for control of the mercury level; the use of a screw clip (S) between the cock and the burette for fine adjustment of the mercury level; calibration of the burette so that, provided a fixed volume is introduced, the % CO_2 can be read direct; an expansion (E) of the tubing above the zero level (Z) on the absorption pipette (A) to decrease the danger of drawing the KOH over into the calibrated burette.

The gas burette is normally 10 ml. but can be smaller. It is surrounded by a water-jacket (J) to improve temperature stability.

The only major departure from Haldane and Graham's apparatus is the omission of the compensating burette. This is tolerable because of the speed of the analysis and the lower level of accuracy required for clinical purposes. No originality is claimed for these modifications, many of which have been noted in one form or another in various laboratories.

The Instrument in Use

Preparation.—The instrument is filled with mercury as follows: take the plunger out of the syringe; put about 12 ml. of mercury in the barrel; replace the plunger; lower and invert the syringe to allow air to collect at the nozzle end; eject the air through the burette; place the syringe in a clip on the back board; adjust the volume of mercury by drawing excess off through tap T with a fine catheter and small syringe. The height of the clip which holds the syringe should be so arranged that, with the cock C open, the mercury level in the burette is below the 0 (that is, 10 ml.) mark. The volume of mercury should be such that, with the plunger of the syringe pushed fully home, the mercury is just below tap T. (A short length of rubber tubing (R) round the piston rod of the syringe provides a buffer to ease the arrest of the mercury at this level when the instrument is in use.) The absorber (10%–20% KOH) is poured into the levelling-bulb (L) until the absorption pipette is filled to the zero mark.

Servicing.—The preparation described above need never be repeated. The only regular servicing required is to maintain a trace of acid (such as 5% sulphuric acid containing an indicator) in the gas burette. Should the KOH be drawn over into the mercury the procedure is as follows: with the tap (⊢), empty the absorption pipette by pouring the KOH off from the levelling-bulb; fill the absorption pipette with dilute acid (for example, 5% sulphuric); turn the tap (T); pass the acid backwards and forwards two or three times; turn the tap (⊢); pour away the acid and refill with KOH; draw the excess acid out of the gas burette with the catheter and syringe. This cleaning and refilling take less than four minutes. If only a small amount of alkali is drawn over, the burette, tap, and adjoining tubing can be cleaned and acidified, using the syringe and catheter, in even less time.

Analysis.—The instrument should be left with the tap (⊣) (this prevents alkali diffusing into the gas burette); turn the tap (⊥) and adjust KOH to zero; turn the tap (⊣); flush the burette with the gas to be analysed (this is most easily done with a three-way tap attached to the top of the burette); draw the sample down to 0 (10 ml.); disconnect from sample (the extra three-way tap facilitates this); turn the tap (T); check that the zero setting has not changed, and wait a few seconds to make sure that the absorber level does not rise—as it will do if the gas burette is contaminated with alkali; pass the gas

over into the absorber and back 10–15 times ; allow the mercury to fall until KOH level returns to zero (this is accomplished by using the cock (C) to regulate rate of fall and the screw clip (S) for final fine adjustment) ; read the % CO_2 off the burette ; repeat passage to check that absorption is complete. The analysis takes less than two minutes from start to finish.

Accuracy.—Serial analyses are reproducible to within ± 0.05%. Several comparisons both with the standard Haldane and with Lloyd's modification (Lloyd, 1958) gave agreement which was usually within ± 0.05% and never outside ± 0.1%. This degree of accuracy is more than adequate for the purpose for which the instrument is intended.

Modified Instrument

The insert shows an alternative arrangement which, at the expense of the complexity of two taps instead of one, slightly speeds up the analyses and facilitates servicing. The calibrated volume includes the bores of the two taps and the connecting tube. The instrument is left with tap 1 (T) and tap 2 (⊥) ; turn tap 2 (⊢) and adjust KOH level to zero. Tap 2 is then turned (⊥) ; the mercury is forced up into the stem of tap 1 and the sample of air is flushed through both taps ; tap 1 is turned (⊣) and the sample is introduced to 0 (10 ml.) ; tap 1 is turned (⊢); tap 2 is turned (⊣); the zero level is checked, and absorption carried out as described above. Cleaning through with acid can be done with tap 2 (⊥) without needing to empty the KOH from the absorption pipette.

I am grateful to Dr. C. J. Dickinson and Dr. J. B. L. Howell for help in developing this analyser, and to Mr. Richard Neave for preparing the illustration. The instruments have been made for me by Aimer Products, Rochester Place, Camden Town, London, N.W.1.

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A Report on Electrical Accidents and their Causes, 1958 (H.M.S.O., price 5s. net), published on December 30, points out that, although it is just 50 years since the Electricity Regulations were made, they still provide an adequate legal basis for the prevention of accidents on premises covered by the Factories Acts, because it has always been possible to interpret them in terms of the current state of electrical engineering science and practice. "Looking back," the report continues, "to the report of the Chief Inspector of Factories for 1907, the year immediately before the Regulations were drafted, it is interesting to note that there were already 264 accidents during the year, of which eight were fatalities. In 1958 the number of accidents had only risen to 714, including 38 fatalities. This is not unsatisfactory, when one considers the enormous increase in electrical supply, and industrial use since that time." Of the 714 accidents which were reported under the Factories Acts, 127 were welders' conjunctivitis or "eye-flash." "Unfortunately," the report records, "the decrease in the number of accidents in 1957 has not been maintained, and this is particularly noticeable when the figures for electrical accidents excluding eye flash are compared for the two years, there having been 527 accidents in 1957 and 587 accidents in 1958. Tables in the report analyse reported accidents by occupation and by causation." (Ministry of Labour Information Service, December, 1959.)

SIMPLE RAPID METHODS OF ESTIMATING ARTERIAL AND MIXED VENOUS pCO_2

BY

E. J. M. CAMPBELL, M.D., Ph.D., B.Sc., M.R.C.P.

AND

J. B. L. HOWELL, Ph.D., M.B., B.Sc., M.R.C.P.
Medical Unit, Middlesex Hospital, London

The aims of this paper are, first, to describe simple rapid methods for estimating mixed venous and arterial pCO_2 and, secondly, to describe an evaluation of their accuracy in clinical disorders in which the carbon dioxide and hydrogen-ion concentration are disturbed.

Physiological and Clinical Significance of Measurements of Blood CO_2 Tension

The arterial CO_2 tension (pCO_2) defines the ratio between metabolism and the effective volume of the breathing—that is, alveolar ventilation.

$$\text{Arterial } pCO_2 \propto \frac{\text{Vol. of } CO_2 \text{ produced}}{\text{Alveolar ventilation}}$$

The ratio between the volume of CO_2 production and alveolar ventilation—and hence the pCO_2—remains relatively constant in health over a wide range of CO_2 production.

If alveolar ventilation is inadequate the pCO_2 rises ; if alveolar ventilation is excessive the pCO_2 falls. The arterial CO_2 tension is a much more reliable measure of effective ventilation than respiratory rate, depth or minute-volume, because these only indicate total ventilation, of which the effective (alveolar) portion is a very variable part.

Proof of inadequate ventilation (ventilatory failure) demands an estimation of arterial pCO_2. Similarly, firm conclusions that treatment has improved ventilation can only be justified by estimations of arterial pCO_2.

The arterial pCO_2 also describes the respiratory component of disturbances in hydrogen-ion regulation—the relationship between *p*H, bicarbonate concentration (which defines the metabolic component), and pCO_2 being expressed in the Henderson–Hasselbalch equation.

$$p\text{H} = \text{pK}' + \log \frac{\text{bicarbonate concentration (mEq/l.)}}{0.03\ pCO_2\ \text{(mm. Hg)}}$$

Respiratory acidosis implies a raised pCO_2 (above 44 mm. Hg). Respiratory alkalosis implies a reduced pCO_2 (below 36 mm. Hg).

The arterial pCO_2 is so informative and unequivocal that it would be measured in the diagnosis and assessment of a wide range of clinical problems were it not for the technical difficulty of its measurement. In this paper we describe a method by which the arterial pCO_2 can be estimated at the bedside in a few minutes by a method requiring little technical skill ; and, if necessary, using very simple and inexpensive equipment.

Methods Employed in Estimation of pCO_2

1. *Arterial Blood*, or arterialized blood (Brooks and Wynn, 1959).—The pCO_2 can be measured (*a*) "directly" by Riley's method (Riley, Campbell, and Shepard, 1957) ; (*b*) "indirectly" by measuring the *p*H and blood CO_2 content and calculating pCO_2 from the Henderson–

Hasselbalch equation; (*c*) with a special electrode (Severinghaus and Bradley, 1958). The analytical techniques are all expensive, difficult, or time-consuming.

2. *"Alveolar" Air.*—In normal subjects the pCO_2 in expired alveolar air is equal to arterial pCO_2. Expired alveolar air can be obtained by the Haldane–Priestley technique or by the use of an end-tidal sampler and analysed, using rapid and simple methods. Unfortunately, the Haldane–Priestley technique requires training and co-operation and the end-tidal sampling methods require special apparatus. Moreover, neither is reliable in patients who have disease of the lungs or who are receiving artificial ventilation, because in such circumstances expired alveolar air has a lower pCO_2 than the arterial blood.

3. *Mixed Venous Blood.*—The pCO_2 of mixed venous blood can be estimated by analysis of alveolar air after this has come into equilibrium with the mixed venous blood. We have reviewed the history and physiological problems of methods based on this principle (Campbell and Howell, 1960), which was originally introduced by Plesch (1909). We concluded that Collier's (1956) method was the most promising for routine clinical use.

Collier's Method

The subject rebreathes from a small (1 l.) bag containing CO_2 (in air or O_2) at a tension estimated to be somewhat higher than that of the mixed venous blood. After two or three breaths the gas in the bag mixes with the alveolar air (whose pCO_2 is lower than mixed venous) to produce a pCO_2 close to that of the mixed venous blood. The venous blood gives off or takes up CO_2 from the mixture until complete equilibrium is reached; and then blood enters and leaves the lungs without changing its pCO_2 and air goes to-and-fro from the bag to the lungs without changing pCO_2. These events must be complete within a time limit set by the circulation, because blood which has left the lungs unable to give off CO_2 passes to the tissues and returns with a higher pCO_2 than previously. About 20 seconds elapse before this recirculation causes the alveolar and bag pCO_2 to start rising.

Collier showed that the equilibrium could be detected as a "plateau" in the record of pCO_2 measured at the mouth with a rapid analyser (Fig. 1 A). If a plateau is not obtained the initial pCO_2 in the bag is considered to be inappropriate and a higher or lower pCO_2 is used, depending on the shape of the record. A trial-and-error procedure such as this is followed until a "good" plateau is obtained. With a suitable range of cylinders containing different CO_2 concentrations, the mixed venous pCO_2 can be determined in less than 10 minutes. Hackney, Sears, and Collier (1958) compared the mixed venous pCO_2 estimated in this way with the arterial pCO_2 in 60 patients, and found it to be, on the average, 6 mm. Hg higher than the arterial. By subtracting this value from the mixed venous pCO_2, the arterial pCO_2 was estimated with a standard error of ± 2.9 mm. Hg and the maximum observed discrepancy was ± 5.3 mm. Hg.

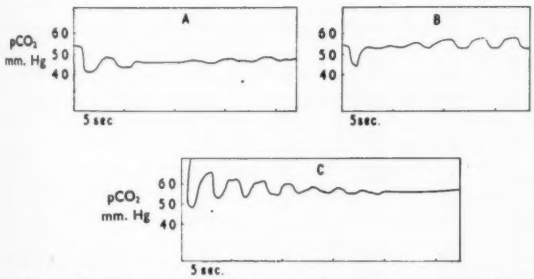

FIG. 1.—Records of pCO_2 at the mouthpiece during rebreathing from a bag of 1.5–2 l. volume. A: Good plateau. B: Bad plateau. Note the early appearance, short duration, and large cyclical variation in subsequent breaths. C: Bad plateau. Note the very late appearance. A was obtained from a normal subject. B was obtained from a patient with emphysema and mild ventilatory failure (arterial pCO_2 55 mm. Hg). C was obtained from a normal subject who rebreathed deeply from a bag containing an initial pCO_2 of 105 mm. Hg (see Discussion).

We have found Collier's method to be excellent, but it necessitates the use of a rapid continuous CO_2 analyser. We have tried to extend its use to circumstances in which such an instrument is not available.

The problems were: (1) to prepare for each subject a CO_2 mixture with a pCO_2 suitable for use as the starting gas for the rebreathing procedure; (2) to see if rebreathing such a mixture for a standard time would give results of an accuracy comparable to that obtained when a continuous record of pCO_2 is available to indicate equilibrium; (3) to see if such a method would be reliable in patients with diseased chests and/or other disorders of CO_2 regulation. We have previously described (Campbell and Howell, 1960) how a CO_2 mixture 4–10 mm. Hg greater than mixed venous blood can be produced in normal subjects by rebreathing 2 l. of 100% O_2 for 90 seconds. In this paper we report an extension of this observation to patients with a wide range of disorders and compare the findings with direct determinations of arterial pCO_2.

Methods

Arterial pCO_2 was measured by Riley's method (Riley *et al.*, 1957) and corrected for temperature (Bradley, Stupfel, and Severinghaus, 1956). Rebreathed gas mixtures were analysed continuously with an infra-red analyser (ird-o-meter) which sampled from the neck of the bag, and at specified times with either a Haldane apparatus or a simplification of it (Campbell, 1960).

Fifteen studies were carried out in the following manner.

Sequence 1.—(A) The subject rebreathed 2 l. of 100% O_2 for 90 seconds. The pCO_2 in the bag was measured. (B) After not less than 2 minutes the subject rebreathed from the same bag for 20 seconds. The pCO_2 in the bag was measured and the continuous record examined for a plateau. Arterial blood was withdrawn 5–10 minutes later.

Sequence 2.—(A) The subject rebreathed 1–1.5 l. of 100% O_2 for 90 seconds. (This reduction in volume was made only if the tidal volume was small enough.) The pCO_2 in the bag was measured. (B) The subject then rebreathed from this bag for 40 seconds. The pCO_2 in the bag was measured and the continuous record examined for a plateau.

Sequence 3 (Carried out only if neither of the previous ones had produced an acceptable plateau).—The subject rebreathed a mixture of CO_2 in O_2 whose pCO_2 was 7–14 mm. Hg above that of the mixed venous blood as estimated in the previous sequences.

We sampled the arterial blood between the first two stages of the study to minimize scatter due to random variations of pCO_2. We were aware that oxygen might cause hypoventilation, but repeated measurements of mixed venous pCO_2 in these patients showed the effect to be negligible. Furthermore, if present, such an effect would make the first estimate of mixed venous pCO_2 appear low in comparison with the arterial pCO_2. The

design of the study was thus biased against the rebreathing method.

The blood and gas measurements were made by separate observers, and no results were revealed until the study was completed.

Subjects.—The diagnosis of each of the patients is indicated in Table I. They were studied in the wards of the hospital by kind permission of the consultant staff. The patient with thyrotoxicosis had a B.M.R. 73% above normal. The patient in diabetic coma had, at the time of the first study, a *p*H of 7.12 and a plasma bicarbonate concentration of 6.3 mEq/l. The patient with renal failure had a plasma bicarbonate concentration of 14 mEq/l. and a haemoglobin concentration of 6 g./l.

Results

The results are presented in detail in Table I, and certain aspects of them are presented in Table II and Figs. 2 and 3.

Rebreathing 2 l. of O_2 for 90 seconds did not always create a pCO_2 in the bag greater than that in the mixed venous blood either in the subjects with an arterial pCO_2 which was abnormally high or in those in whom it was low. Furthermore, rebreathing the CO_2 mixture so prepared did not yield a "good" plateau in most of the subjects. However, rebreathing this mixture for 20 seconds did produce a pCO_2 in the bag about 6 mm. Hg greater than the arterial pCO_2 whether or not a plateau was obtained.

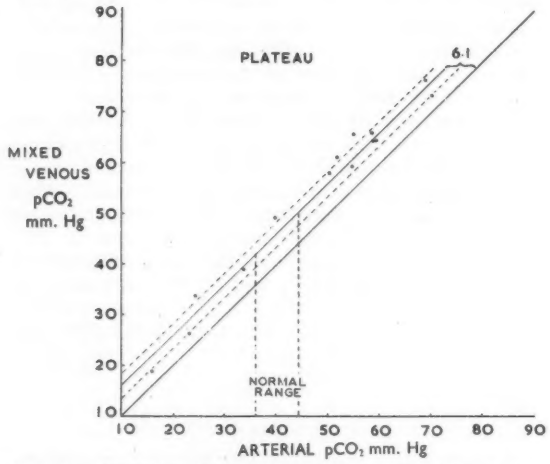

FIG. 2.—Comparison between the mixed venous pCO_2 as estimated from the plateau obtained with the continuous analyser and the arterial pCO_2.

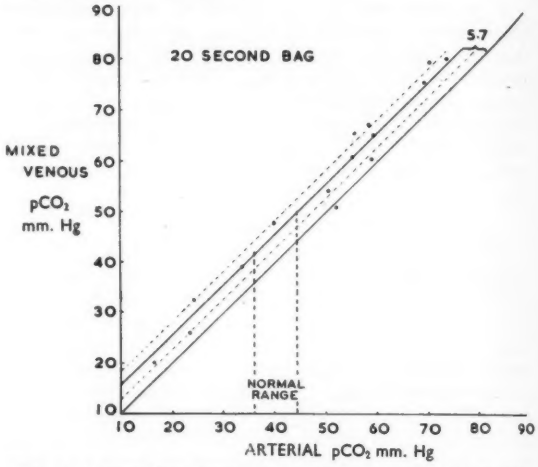

FIG. 3.—Comparison between the mixed venous pCO_2 as estimated from the bag at the end of sequence 1 ("20-seconds bag") and the arterial pCO_2.

TABLE I.—*Results. The Order in Which these Measurements were Made is Explained in the Text*

Study	Age	Sex	Diagnosis	Sequence	Initial Gas Composition			Volume (l.)	Rebreathing Period (secs.) *A*	pCO_2 (mm. Hg)	Rebreathing Period (secs.) *B*	pCO_2 (mm. Hg)	Plateau pCO_2 (mm. Hg)	Arterial pCO_2 (mm. Hg)
					O_2 %	CO_2 %	pCO_2 (mm. Hg)							
1	58	F	C.B. and E.+P.	1	100			2·0	90	58·0	20	60·5	X	
				2	100			1·25	90	67·5	40	67·0	64·0	59·0
2	71	F	,,	1	100			2·0	90	75·0	20	79·0	73·0	
				2	100			1·25	90	83·0	40	84·0	X	70·5
3	61	F	,,	1	100			2·0	90	65·0	20	61·0	61·0	
				2	100			1·5	90	62·0	40	64·0	59·0	55·0
4	32	F	Ren. F.	1	100			2·0	90	35·0	20	32·0	33·0	
				2	100			1·5	90	36·0	40	34·0	X	24·0
5	58	M	C.B. and E.+P.	1	100			2·0	90	50·5	20	51·0	X	
				2	100			1·5	90	57·0	40	56·0	X	
				3	89·5	10·5	75	1·5					61·0	52·0
6	75	F	,,	1	100			2·0	90	66·0	20	66·0	65·0	
				2	100			1·5	90	69·0	40	73·0	X	55·5
7	69	M	C.B. and E.+P. +fibrosis	1	100			2·0	90	63·0	20	65·0	X	
				2	100			1·5	90	70·0	40	73·0	64·0	59·5
8	69	M	,,	1	100			2·0	90	76·0	20	80·0	X	
				2	100			1·5	90	75·0	40	82·0	X	73·5
9	69	M	,,	1	100			2·0	90	77·0	20	76·0	X	
				2	100			1·5	90	80·0	40	80·0	76·0	69·0
10	44	F	C.B. and E.+P.	1	100			2·0	90	56·0	20	54·0	X	
				2	100			1·5	90	58·0	40	61·0	X	
				3	91·8	8·2	58	1·5					58·0	50·5
11	65	M	D.I.F.	1	100			2·0	90	44·5	20	39·0	39·0	33·5
12	64	M	C.B. and E.+P.	1	100			2·0	90	67·5	20	67·5	X	
				2	100			1·5	90	67·0	40	70·0	X	
				3	89·5	10·5	75	1·5					65·5	58·5
13	16	F	Diab. coma	1	100			2·0	90	21·0	20	20·0	19·0	16·0
14	16	F	,, ,,	1	100			2·0	90	30·0	20	26·0	26·0	23·0
15	31	F	Thyrotox.	1	100			2·0	90	53·0	20	48·0	49·0	40·0

C.B. and E.+P.=Chronic bronchitis and emphysema plus pneumonia. Ren.F.=Renal failure. D.I.F.=Diffuse interstitial fibrosis of the lungs.
X=Plateau not obtained.

TABLE II

Difference between (*a*) Arterial pCO_2 (Riley) and (*b*) pCO_2 Estimated by:	Mean (*b*–*a*)	S.D.	Range
Plateau	6·1	2·4	+2·5 to + 9·5
20-sec. bag (Sequence 1B)	5·7	2·9	−1 ,, +10·5
40- ,, ,, ,, 2B)	10·7	3·5	+4 ,, +17·5
90- ,, ,, (2 l.) (Sequence 1A)	5·9	5·3	−1·5 ,, +13
90- ,, ,, (1–1·5 l.) (Sequence 2A)	8·9	3·6	+1·5 ,, +13·5

When the initial volume of the bag was reduced to 1–1.5 l. the pCO_2 after 90 seconds usually exceeded mixed venous pCO_2. "Good" plateaux were not, however, obtained more often during the subsequent rebreathing than were obtained in sequence 1.

One or other of the three sequences yielded a good plateau in all but one of the studies. In the one exception a plateau seemed to have been obtained, but subsequent examination showed that the criteria laid down later (see Discussion) were not fulfilled. In the other studies the plateau pCO_2 was on average 6.1 mm. Hg greater than arterial (S.D. 2.4; range +2.5 to +9.5).

The 40-seconds rebreathing period at the end of sequence 2 produced a pCO_2 in the bag 10.7 mm. Hg greater than arterial pCO_2 (S.D. 3.5; range +4 to +17.5). This prolonged rebreathing period was included in the study because we believed that in patients with hypoventilation the equilibration with mixed venous blood might not occur in 20 seconds and this might lead to a serious underestimate of mixed venous pCO_2. Our earlier studies of normal subjects had shown that the effect of recirculation (see above) was to cause only a small rise in the bag pCO_2 (2–3 mm. Hg between 20 and 40 seconds). If the 40-seconds period at the end of sequence 2 produced a pCO_2 in the bag which greatly exceeded that produced by the 20-seconds period in sequence 1, we anticipated that the 20-seconds value would be found to underestimate the mixed venous pCO_2 more than the 40-seconds value overestimated it. In none of these patients was this found to be so. However, it may yet be found in patients with extremely high pCO_2 values that the procedure according to sequence 2 is a valuable check on the standard procedure (that is, sequence 1).

Discussion

The failure of the initial rebreathing procedure in sequence 1 to produce a pCO_2 above that of mixed venous blood is readily understandable in the subjects with a raised blood pCO_2. More CO_2 had to be added to the bag than in normal subjects, and the patients all had diseased lungs with an increased lung volume and poor distribution of the inspired air. The failure of the subjects with reduced pCO_2 values to produce a high pCO_2 in the bag by the initial procedure is less immediately understandable. Further work suggests that the finding may be due to the distribution of the CO_2 formed in the actively metabolizing tissues in a larger effective "space" than is initially available in normal subjects. The blood-flow through many tissues in patients with anaemia or acidosis is probably greater than in normal subjects, and this will distribute the CO_2 throughout the body more rapidly.

The arteriovenous pCO_2 difference of about 6 mm. Hg, which we have found is the generally accepted value, the important consideration being that at rest it is small and relatively unaffected by changes in cardiac output (Suskind and Rahn, 1954).

Our results, in agreement with those of Hackney *et al.* (1958), show that the arterial pCO_2 can be estimated by subtracting 6 mm. Hg from mixed venous pCO_2 as estimated by the rebreathing technique. In comparing our estimates of arterial pCO_2 with the direct measurements four factors must be considered, all of which would tend to magnify the scatter of the results. (1) The arterio-mixed-venous pCO_2 difference probably varies slightly. (2) The rebreathing method measures the pCO_2 of "oxygenated" mixed venous blood rather than true mixed venous blood. The operation of the Christiansen–Douglas–Haldane effect causes the "oxygenated" mixed venous pCO_2 to be about 2 mm. Hg greater than the true value, this difference being greater when the cardiac output is low or when the alveolar and blood O_2 tensions are low (Campbell and Howell, 1960). (3) The mixed venous and arterial pCO_2 estimations could not be made simultaneously because the rebreathing procedure raises the arterial pCO_2. This means that temporal variation in arterial pCO_2 would add to the random error. The magnitude of this variation is not known but is probably greater in patients with ventilatory failure than in subjects with low or normal pCO_2. (4) The direct determination of arterial blood pCO_2 by Riley's method has a standard error of $\pm$1.7 mm. Hg (Shepard and Meier, 1957). When these factors are considered, the agreement between the direct arterial pCO_2 measurements and the estimations from the rebreathing method is good.

The results with the modified Collier technique, using the rapid CO_2 analyser and also using the simplified procedure, are in good agreement with those obtained by Hackney *et al.* (1958). In routine clinical use our experience has confirmed the statement by Griggs *et al.* (1958): "the 'rebreathing method' offers a simple reliable test for ventilatory failure which can be performed on the ward by a technician in less than 10 minutes. It can be performed on all types of patient, even on those who are comatose or confused." The demonstration that a rapid CO_2 analyser, though allowing the equilibration process to be visualized and making the procedure somewhat quicker, is not essential has, we feel, brought the measurement of pCO_2 into the realm of simple bedside techniques.

Practical Difficulties.—The only practical difficulty we have encountered is the prevention of leaks at the mouthpiece in unco-operative edentulous patients. We have been able to overcome this either by the use of an "everseal" anaesthetic mask or by the use of a mouthpiece with a large (4 by 2 in.; 10 by 5 cm.) flange. After putting this in the mouth it can be pulled outwards and the lips held down on to it.

Analytical Difficulties.—The simple chemical analyser we used presented no difficulties. Occasionally there was difficulty in deciding during Collier's procedure, using the rapid CO_2 analyser, whether or not a plateau had been obtained. Hackney *et al.* (1958) define a satisfactory plateau as "an expired CO_2 concentration that varied less than 0.1% CO_2 from the preceding inspired concentration achieved within 20 seconds after the start of rebreathing." We have quite often obtained records which fulfil this criterion but which would have given values too low (Fig. 1 B). A phase-reversal of the CO_2 concentration at the mouthpiece may occur as the air in the bag and in the lungs is mixed, and may mimic

a plateau. Less commonly we have also seen apparent plateaux when too high an inspired CO_2 concentration was used. This may occur in patients breathing very shallowly, when it is apparently due to inadequate exchange between the bag and the lungs; the gas in the neck of the bag and in the subject's dead space just passing to-and-fro by the sampling site. An extreme example, of course, is apnoea, which can be excluded by watching the movements of the bag. We have also observed an apparent plateau about 20–25 seconds after the start of rebreathing in subjects who breathe deeply when very high inspired CO_2 concentrations are used (Fig. 1 C). The probable explanation of this late plateau is that there is too much CO_2 to be removed by the blood before recirculation. Equilibration therefore occurs with recirculated blood whose pCO_2 was raised by the very high alveolar pCO_2 present in the first 5–10 seconds.

As a result of these findings we suggest the following modification of Collier's definition of a satisfactory plateau: an inspired-expired CO_2 concentration difference of less than 0.1% which is present in two successive breaths. Plateaux which occur within two breaths of the start of rebreathing or which take more than 15 seconds to appear should be regarded with suspicion.

Conclusions

The mixed venous and arterial CO_2 tensions can be estimated accurately by rebreathing techniques.

The simplest method is to use a continuous CO_2 analyser as described by Collier.

If such an instrument is not available it is still possible to estimate pCO_2 with sufficient accuracy for clinical purposes in 5 to 10 minutes, using the following procedure: (1) Fill a bag with 1.5–2 l. of oxygen. (2) Rebreathe one and a half minutes. During first few breaths partially empty bag if tidal volume is less than half bag-volume. (3) Wait two minutes. (4) Rebreathe 20 seconds or five breaths (whichever is longer). (5) Analyse: bag pCO_2 = mixed venous pCO_2 (arterial approximately 6 mm. Hg less). [*Note:* (*a*) If in doubt, make 1 smaller; extend 2 as long as possible; extend 4 to 40 seconds. These should not increase bag pCO_2 by more than 5 mm. Hg. (*b*) pCO_2 of bag after initial one and a half minutes' rebreathing will give an approximate estimate of mixed venous pCO_2 (Table II).]

Summary

The physiological significance of the measurement of arterial pCO_2 is summarized and previous methods are reviewed.

Collier's rebreathing method for the estimation of the mixed venous and arterial CO_2 tensions is outlined.

A simplification of Collier's method, eliminating the necessity for a continuous record of CO_2 concentration, is described.

An evaluation of the method is described in patients with various disorders of CO_2 and *p*H regulation showing that the accuracy is to within ± 3 mm. Hg.

Simple routines for the estimation of pCO_2 are described for use both with and without continuous analysis of CO_2.

We are grateful to Dr. A. Willcox, Professor A. Kekwick, Dr. G. D. Hadley, Dr. F. H. Scadding, and Dr. J. D. N. Nabarro for permission to study patients under their care; and to Professor Kekwick for reading the manuscript.

The ird-o-meter was kindly lent to us by the Infra Red Development Co., Welwyn Garden City, Herts.

ADDENDUM.—Since this paper was prepared the method has been used for detecting the presence or absence of ventilatory failure in the following conditions: chronic bronchitis and emphysema, asthma, pneumonia, poliomyelitis, barbiturate poisoning, carbon-monoxide poisoning, head injury, cerebrovascular accidents, heart failure, myasthenia gravis, peripheral neuritis, post-anaesthetic collapse, post-thoracotomy distress, obesity, hypothyroidism, polycythaemia, and carcinoma of the bronchus. In several patients decisions about the use of artificial ventilation, tracheostomy, or other measures depended on the findings. It has also been used to evaluate the disordered hydrogen ion regulation of patients with diabetic coma, renal failure, pyloric stenosis, Addison's disease, Cushing's syndrome, potassium depletion, uretero-colic anastomosis, steatorrhoea, and tetany. Many of these measurements were made by junior medical staff or students.

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CHANGES IN FORCED EXPIRATORY VOLUMES THROUGHOUT THE DAY

BY

H. C. LEWINSOHN, M.B., B.Ch.
Medical Registrar, London Chest Hospital

L. H. CAPEL, M.B., M.R.C.P.
Senior Medical Registrar, London Chest Hospital

AND

J. SMART, M.D., F.R.C.P.
Consultant Physician, London Chest Hospital

The early-morning exacerbation of their symptoms is often the bitterest complaint of patients suffering from chronic productive cough and breathlessness. The important immediate cause of this chronic breathlessness is probably persistent airway obstruction. An increase in the severity of this obstruction may cause the early-morning increase in breathlessness. This study was undertaken to show the magnitude of the change in the airways, and to find out whether it is peculiar to obstructive airway disease or whether it is part of a cycle of changes throughout the day present both in health and in airway disease.

Methods and Results

Five healthy men (mean age 30 years; mean forced expiratory volume 3,270 ml.) and 16 male patients with obstructive airway disease, 12 severely affected (mean

age 57 years; mean forced expiratory volume 760 ml.), and four mildly affected (mean age 48 years; mean forced expiratory volume 2,190 ml.) were tested. In each patient the diagnosis of chronic bronchitis and emphysema, with or without asthma, had been made. The patients were admitted to hospital for 48 hours, usually at the week-end to avoid loss of work if the patient was working.

Two measurements were made with a recording spirometer—the volume of air expelled during the first second and that expelled during the completion of a forced expiration following a full inspiration. These are, respectively, the forced expiratory volume (F.E.V.) and the forced vital capacity (F.V.C.). These were recorded at fixed times during the day, including 10 p.m. and 6 a.m. No medicines were taken.

The results in each case and the mean of the results of each group are shown graphically in Figs. 1, 2, and 3.

At 6 a.m. the F.E.V. and the F.V.C. were lower than at any other time of the day both in healthy subjects and in patients. By 8 a.m. the mean increase in the F.E.V. was 2.9% in the healthy subjects. By 9 a.m. it was 60% and 36% respectively in the patients with mild and with severe obstructive airway disease. Similar changes were seen in the F.V.C.

Relatively large spontaneous variations in the F.E.V. and the F.V.C. occurred between 9 a.m. and 5 p.m. in the patients.

Discussion

The changes in the F.E.V. and the F.V.C. probably reflect changes in the severity of airway obstruction and possibly changes in total lung capacity as well. Total lung capacity may fall because of an increase in the volume of blood in the lungs or a decrease in the number of patent alveoli occurring during sleep. Alterations in expiratory force are probably of minor importance; a greater expiratory force which might increase the F.E.V. would reduce the F.V.C. (the vital capacity of patients with obstructive airway disease is greater when expelled without force). In fact, the F.E.V. and the F.V.C. varied together. Failure to inspire to maximum depth would reduce both the F.E.V. and the F.V.C. This was prevented so far as possible by carefully briefing the subjects.

Between 10 p.m. and 9 a.m. the pattern of change was the same for each subject—a marked dip and rise of the F.E.V. and the F.V.C. Not all patients expectorated in the morning. In those who did, improvement in spirometry was not related to the volume or character of the sputum, but often followed expectoration immediately.

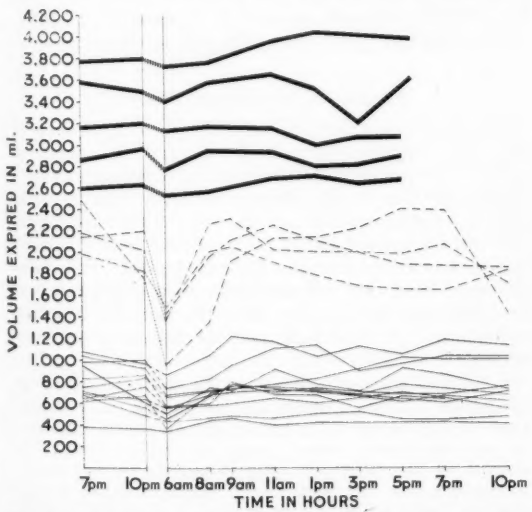

FIG. 1.—Changes in the F.E.V. during the day in normal, mildly affected, and severely affected subjects. ▬▬: Normal. - - - -: Mild. ———: Severe.

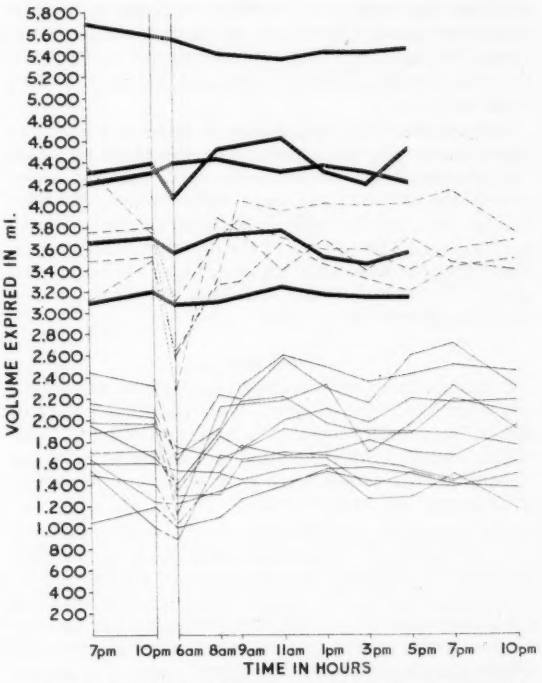

FIG. 2.—Changes in the F.V.C. during the day in normal, mildly affected, and severely affected subjects. ▬▬: Normal. - - - -: Mild. ———: Severe.

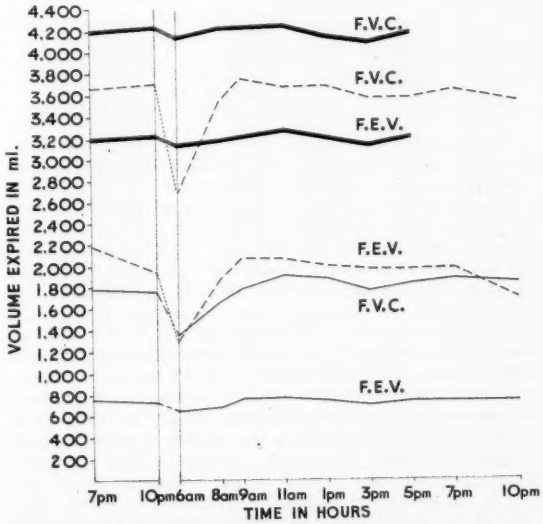

FIG. 3.—Changes in the mean F.E.V. and the mean F.V.C. during the day in normal, mildly affected, and severely affected subjects. ▬▬: Normal. - - - -: Mild. ———: Severe.

Between 9 a.m. and 10 p.m. the pattern of change was different in each subject. The F.E.V. of the mildly disabled patients and the F.V.C. of some of the severely disabled patients varied in a regular manner. Other changes appeared random (Figs. 1 and 2). A number of patients showed a distinct fall in the F.V.C. after the midday meal.

These changes were recorded during a day spent in hospital. McKerrow *et al.* (1958) have shown that the F.E.V. of cotton-workers falls during their day in the dust of the mill. In contrast, coal-miners slightly increased their F.E.V. during the shift at the coal-face. These investigators also give experimental evidence for the relationship between the F.E.V. and airway resistance.

Patients shown by spirometry to have severe airway disease may be but moderately disabled by effort breathlessness. A comparatively small increase in the airway obstruction may then cause severe disability (Capel and Smart, 1959). Such an increase occurs during sleep. The severity of the morning breathlessness may therefore reflect the magnitude of the permanent airway obstruction rather than the magnitude of the morning deterioration alone.

Conclusion

Relatively large spontaneous variations in the F.E.V. and the F.V.C. of patients with obstructive airway disease may occur between 9 a.m. and 5 p.m. This might affect the interpretation of results when serial changes in these volumes are used to measure the action of drugs on the bronchial tree.

The early-morning decrease in the F.E.V. and the F.V.C. was found to be part of a cycle of changes occurring throughout the day both in health and in generalized obstructive airway disease. The decrease was greater in patients with airway disease. The severity of the resulting increase in breathlessness probably reflects the magnitude of permanent obstructive airway disease rather than the magnitude of the temporary decrease in the F.E.V. and the F.V.C.

We thank Dr. K. F. W. Hinson for his help in the preparation of the manuscript.

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A scheme for the disposal of radioactive wastes used in Edinburgh for medical and research work has been agreed upon by the university, the Department of Health for Scotland, and the trade unions representing employees who will handle the waste. It covers disposal into sewers, municipal tips, and ocean dumping. Liquid wastes are kept in store until their radioactivity has exhausted itself, and then they are disposed of in the city sewers—with the safeguard that the maximum level of radioactivity is the same as that permitted in drinking-water. A further dilution takes place immediately the wastes enter the sewers, which discharge into the Forth estuary. Solid wastes of short-lived materials are wrapped securely in a strong paper bag and placed in a padlocked dustbin. This is taken to a corporation rubbish tip, where the dustbin is unlocked and the parcel dropped into a pit; this pit is then filled in. Materials much more "hot" in the radioactive sense are used in the university, chiefly for experiments. When these have to be disposed of the Department of Health will arrange for their dumping in the Atlantic. (*Glasgow Herald*, February 4.)

SYSTEMIC AND LOCAL CORTICOSTEROID THERAPY IN ULCERATIVE COLITIS

BY

S. C. TRUELOVE, M.D., M.R.C.P.

Nuffield Department of Clinical Medicine, University of Oxford

(*From the Radcliffe Infirmary, Oxford*)

During the past decade it has been established that corticosteroids improve the chance of obtaining clinical remission when an attack of ulcerative colitis is being treated medically. However, there are two main ways of using corticosteroid therapy in this disease. On the one hand, cortisone and its analogues may be used systemically. On the other, they may be applied locally within the colon with the intention that their action shall be chiefly a direct one upon the inflamed mucosa.

Both these methods of employing corticosteroid therapy in ulcerative colitis have been shown to be beneficial. So far as oral cortisone is concerned, a large-scale "blind" controlled trial carried out with the co-operation of a number of physicians showed that patients receiving cortisone were nearly three times as likely to be in clinical remission within six weeks of starting medical treatment as were patients in the control group (Truelove and Witts, 1954, 1955). Local corticosteroid treatment has likewise been shown to be of value. Two independent controlled studies, using the water-soluble compound, hydrocortisone hemisuccinate sodium, as a nightly rectal drip, have provided convincing evidence that rapid remissions are often obtained in the less severe attacks of ulcerative colitis (Truelove, 1958; Watkinson, 1958).

There is plainly a need to know which of these two methods of using corticosteroids is to be preferred. Though neither has been shown to reduce the risk of subsequent attacks of ulcerative colitis, it is of consequence to know which is the more likely to bring an attack to an abrupt halt. If attacks of the disease can be checked promptly, many of its dangers disappear even though no permanent cure has yet been found.

Objects of the Present Study

The first object was to assess the relative efficacy of oral and local corticosteroid therapy in ulcerative colitis. The second object was to test a personal clinical impression that combined therapy with both systemic and local corticosteroid is better than either used alone. This impression was based on experience with a number of patients whose symptoms were unchanged by systemic and local corticosteroid treatment used singly but who went into clinical remission when the two methods were combined. The following may be taken as a typical example.

A medical student aged 22 was seen in August, 1957, because of bloody diarrhoea for the previous two months. There was a history of a bad attack of bloody diarrhoea 10 years previously which lasted for three months. In between he had been well. Sigmoidoscopy showed typical ulcerative colitis with hyperaemia, granularity, and contact bleeding. A barium enema showed contour irregularities of the rectum and sigmoid colon. Local hydrocortisone hemisuccinate sodium for two weeks gave no benefit, either

symptomatically or sigmoidoscopically. He was then given prednisolone by mouth, 5 mg. q.d.s. Once again his condition was unchanged. The two types of treatment were then combined, and he showed rapid improvement, was symptom-free in a fortnight, and had normal sigmoidoscopic appearances. Since 1957 he has had two further recurrences of the disease, but both were stopped in about 10 days by the use of combined corticosteroid treatment.

Selection of Patients

The patients chosen were all suffering from an attack of ulcerative colitis with sigmoidoscopic evidence of active disease. In the case of first attacks of the disease a barium enema also showed evidence of active disease. In the case of relapse of established disease a barium enema was not always carried out before treatment, but previous examinations had shown unequivocal evidence of ulcerative colitis.

Patients in whom the disease was confined to the rectum and recto-sigmoid junction (haemorrhagic proctitis) were not included. Those who had very severe attacks of ulcerative colitis were also excluded; such patients, who were defined as those in whom a profuse bloody diarrhoea was accompanied by serious constitutional symptoms or by major complications of the disease, were treated along more vigorous lines in hospital. Thus the patients considered here were examples of classical ulcerative colitis presenting as an attack of mild or moderate severity.

Treatment Groups

As the patients presented, they were allotted at random to one or other of three main types of treatment.

(*a*) *Oral Prednisolone*, in a dose of 5 mg. q.d.s., was given to one-third of the patients. This dose was chosen because from the outset the intention was to treat as many as possible on an out-patient basis, and this dose has appeared to be a safe one to use in such circumstances.

(*b*) *Local treatment*, administered as a nightly rectal drip, was given to another one-third of the patients. It was arranged in advance that in half of these patients the corticosteroid would be hydrocortisone hemisuccinate sodium, while the other half would have prednisolone 21-phosphate. This permitted an internal comparison, within this group, of two different corticosteroids used locally. The practical details for the use of a nightly rectal drip have been given in previous articles (Truelove, 1956, 1957). Hydrocortisone hemisuccinate sodium was given in a daily dose of 100 mg. of hydrocortisone. The prednisolone 21-phosphate drip was made by dissolving special tablets of this agent in tap-water, the daily dose being 40 mg. of prednisolone.

(*c*) *Combined treatment* was given to the remaining one-third of the patients. All these were given prednisolone by mouth in a dose of 5 mg. q.d.s. together with local treatment in the form of a nightly rectal drip. Half the patients used hydrocortisone hemisuccinate sodium as their local treatment, while the other half used prednisolone 21-phosphate.

Results

The results of 120 courses of treatment are now reported, there having been 40 of each of the three main types of treatment given. Since the trial took nearly two years to execute, some patients who were treated successfully in the early stages were later seen with a recurrent attack and were readmitted to the trial and assigned at random to one of the treatment groups. The actual number of patients concerned in the trial was 105.

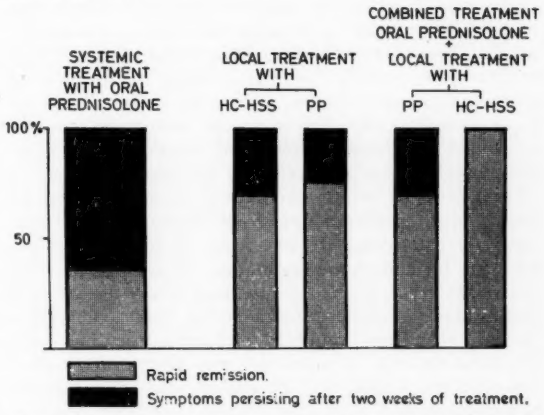
The effects of treatment have been assessed by determining how many patients went into rapid clinical remission with the various treatments used. A rapid clinical remission was defined as complete loss of any symptoms within two weeks of starting treatment and with the sigmoidoscopic appearances showing a decisive improvement.

The Table and Chart show the results obtained. With oral prednisolone, about one-third of the patients were in clinical remission at the end of the two-week trial period. With local treatment used alone, approximately three-quarters of the patients had a rapid remission. There is little to choose between hydrocortisone hemisuccinate sodium and prednisolone 21-phosphate when used alone as local therapy. The difference between local therapy and systemic therapy is highly significant in a statistical sense; if the results for the two types of local treatment are considered as a single unit, which

Results of Treatment, Showing the Number of Patients Going into Rapid Remission with the Various Treatments

Type of Treatment	No. of Patients	No. Symptom-free at End of 2-Weeks Treatment
Systemic Treatment:		
Prednisolone by mouth	40	14 (35%)
Local Treatment:		
Nightly rectal drip:		
(*a*) With hydrocortisone hemisuccinate sodium	20	14 (70%)
(*b*) With prednisolone 21-phosphate	20	15 (75%)
Combined Treatment:		
Prednisolone by mouth combined with a nightly rectal drip:		
(*a*) With prednisolone 21-phosphate	20	14 (70%)
(*b*) With hydrocortisone hemisuccinate sodium	20	20 (100%)

Statistical Significance of the Differences.—Both types of local treatment give significantly more rapid remissions than oral prednisolone ($P=0.01$). Combined treatment with oral prednisolone and local prednisolone 21-phosphate is similar to local treatment used alone. Combined treatment with oral prednisolone and local hydrocortisone hemisuccinate sodium is significantly better than local treatment used alone. (An exact test of significance gives a value of $P=0.024$ when this treatment is compared with the best other treatment.)



The different proportions of patients with rapid remission of symptoms according to the type of corticosteroid therapy. (HC-HSS = Hydrocortisone hemisuccinate sodium. PP = Prednisolone 21-phosphate.)

gives 29 rapid remissions out of 40 treatments, this difference from the results obtained by oral prednisolone would occur by chance less often than once in a thousand times. It can therefore be taken as adequately proved that local corticosteroid therapy is much more efficient in producing rapid clinical remission of an attack of ulcerative colitis than is systemic corticosteroid therapy, at any rate in the doses used in this study.

With combined systemic and local treatment, a somewhat surprising result emerges. When oral prednisolone is given in conjunction with local treatment with prednisone 21-phosphate the proportion of rapid clinical remissions is similar to that obtained with local treatment used alone. On the other hand, when oral prednisolone is combined with local treatment with hydrocortisone hemisuccinate sodium every patient so treated in the present study had a rapid clinical remission. This difference is statistically significant. There is therefore a prima facie case for regarding the combination of oral prednisolone with local hydrocortisone hemisuccinate sodium as demonstrably more efficient in an attack of ulcerative colitis than any other treatment tested in the present study.

Discussion

The results presented have both practical and theoretical implications.

On the practical side, topical use of corticosteroids within the colon has proved decisively more effective in aborting attacks of ulcerative colitis than oral prednisolone in the dose used. The local method of application enjoys the additional advantage that side-effects of corticosteroid therapy do not appear to arise. It is therefore recommended that, for the truly mild attack of ulcerative colitis, initial treatment should consist of local corticosteroid therapy, and either hydrocortisone hemisuccinate sodium or prednisolone 21-phosphate can be used in the equal expectation that most of the attacks will be checked. For the minority of mild attacks which fail to show a rapid response to local treatment used alone, combined treatment with oral prednisolone and local hydrocortisone hemisuccinate sodium should be employed. The same combination should be used from the outset in those attacks which are bad enough to be classed as of moderate severity, by which is implied an attack with profuse bloody diarrhoea but without serious constitutional disturbances. In such attacks the necessity for halting the symptoms as quickly as possible outweighs the minor risks involved in the use of oral prednisolone in the dose used in this study. Once the patient has been rendered symptom-free the oral prednisolone can be tailed off and discontinued after two or three weeks, and the risk of immediate relapse is negligible.

Though the present trial period lasted for only two weeks, it should not be supposed that treatment ceased as soon as this time elapsed. It has appeared to be beneficial to continue with nightly local treatment for at least several weeks once a clinical remission has been obtained, because there is a strong suggestion that such a procedure diminishes the chance of a recurrent attack in the succeeding months. At present the data are inadequate for a definite statement, but in due course it will be possible to settle the point with some precision, and the relevant facts will then be reported.

So far as the results obtained with oral prednisolone are concerned, it may be contended that the results would have been better if a larger dose had been used. This is probably true, but doses appreciably larger than the one used are apt to cause a greater number of complications of treatment and should therefore be avoided if possible. The aim in the present study was to compare corticosteroids in doses that previous experience had shown to be safe in routine use, even with out-patients. It can also be mentioned that in the large-scale controlled trial of oral cortisone a dose of 25 mg. q.d.s. (which corresponds roughly to the dose of prednisolone used in the present study) was given in the first half of the trial period, while physicians could use up to 75 mg. q.d.s. in the second half. There was little additional benefit from giving the higher doses, though this point was not dealt with in the published report by Truelove and Witts (1954, 1955).

Severe attacks of ulcerative colitis were not included in the present study. Such attacks demand much more intensive treatment, including blood transfusion and control of electrolyte balance, than the present patients received. Nevertheless, it can be said that, *mutatis mutandis*, the principles of treatment which emerge from studying the less severe attacks apply also to the more severe. Combined systemic and local treatment has been used in a considerable number of severe attacks in Oxford and the results appear to represent an advance on previous medical therapy. However, there are various technical points requiring attention when severe attacks are treated with local corticosteroids, and these will be dealt with in a separate communication.

The fact that the great majority of the less severe attacks of ulcerative colitis can now be aborted by medical treatment has important practical implications in the management of the disease. In the case of first attacks the aim should be to diagnose the disease at the earliest possible moment so that treatment can be started with minimal delay. Most of the first attacks begin gradually, with symptoms worsening over the course of weeks or even months. Until the advent of modern medical measures, such patients had almost as bad a prognosis as those in whom the first attack began abruptly with the rapid development of a severe illness, and the fatality rate in the first attack was high (19% reported by Rice-Oxley and Truelove (1950); 46% reported from Switzerland by Demole (1956); 18% reported by Kellock and White (1957): all these figures referring to patients treated in hospitals). The need is to exclude infective dysentery and focal lesions, such as carcinoma coli and diverticulitis, and to obtain the sigmoidoscopic and radiological evidence of ulcerative colitis as quickly as possible so that appropriate treatment can be given before the patient becomes seriously ill. With established disease it is probably best if the patient remains in touch with a physician who has a special interest in the disease, so that any relapse can be treated promptly, while those who fail to do well can be selected for surgery.

From a theoretical standpoint it is of interest that combining systemic prednisolone with local prednisolone 21-phosphate gave results no better than using local corticosteroids alone, whereas combining systemic prednisolone with local hydrocortisone hemisuccinate sodium gave the best results in the trial, being effective in all the 20 patients so treated. There seem to be two main possibilities to account for this finding. The first is that prednisolone 21-phosphate differs from hydro-

cortisone hemisuccinate in physical or simple chemical properties in such a way that its local action in the colon is different. So far as hydrocortisone is concerned there is evidence that the amount of absorption which occurs when it is introduced into the colon is largely dependent upon the chemical nature of the particular hydrocortisone preparation used.

Nabarro *et al.* (1957) based their estimate of absorption on the amount of metabolites of hydrocortisone excreted in the urine. They found evidence that hydrocortisone in the form of the free alcohol was absorbed in considerable amounts. Hydrocortisone acetate was but little absorbed, a finding which might be related to its very low solubility in water. Hydrocortisone hemisuccinate sodium was likewise poorly absorbed, a finding not to be explained on the basis of low aqueous solubility, because this compound is highly soluble in water. Schwartz *et al.* (1958), using hydrocortisone labelled with ^{14}C, have shown that when the hemisuccinate is applied topically within the colon there is no appreciable change in the level of circulating hydrocortisone in the blood; in other words, the presumptive conclusion is that the beneficial action of topical hydrocortisone hemisuccinate in ulcerative colitis is a local one upon the mucosa. Comparable information is not available for prednisolone 21-phosphate.

The other possibility is that prednisolone and hydrocortisone have a truly synergistic action at tissue level, but this must be regarded as highly speculative, as there do not appear to have been any systematic studies of the use of combinations of different corticosteroids as therapeutic agents. There is work in existence which demonstrates the possibility of such a synergistic action. A lengthy review by Veldstra (1956) on synergism and potentiation, with special reference to the combination of structural analogues, takes into account a number of ways in which a truly synergistic action could occur between two closely related substances such as prednisolone and hydrocortisone. In particular, Veldstra brings forward much evidence to support his view that synergism may occur when the components of a mixture are acting "in series" towards the same end-effect—for example, when antimetabolites are competing with different intermediates in a biosynthetic chain.

In this connexion it is of great interest that Nugent *et al.* (1959) have brought forward evidence that different metabolic pathways are involved in the breakdown of hydrocortisone and prednisolone in the body. It therefore appears that the possibility of obtaining synergistic action by using mixtures of different corticosteroids is a topic which deserves systematic study quite outside any applications there may be in the particular disease, ulcerative colitis, now being discussed.

Summary

A comparative study of different types of corticosteroid therapy has been made to determine their relative efficacy in bringing about a rapid clinical remission in ulcerative colitis of mild or moderate severity. A rapid clinical remission is defined as complete loss of symptoms within two weeks of starting treatment and with decisive improvement in the sigmoidoscopic appearances.

Patients were allotted at random to one or other of three treatments: (1) Prednisolone by mouth in a dose of 5 mg. q.d.s. (2) Local treatment with a water-soluble corticosteroid applied by means of a nightly rectal drip. Two different corticosteroids were used—namely, hydrocortisone hemisuccinate sodium and prednisolone 21-phosphate. (3) Combined systemic and local treatment, in which the patients received oral prednisolone in a dose of 5 mg. q.d.s. and a nightly rectal drip of either hydrocortisone hemisuccinate sodium or prednisolone 21-phosphate.

The results obtained in 120 courses of treatment are presented, there being 40 patients in each of the three main treatment groups.

About one-third of the patients treated with oral prednisolone went into rapid clinical remission. With local corticosteroid treatment nearly three-quarters of the patients had a rapid clinical remission. There is little to choose between the two corticosteroids used for local treatment, each of them being much more effective than oral prednisolone in the dose used.

With combined systemic and local treatment the results depended upon the particular combination used. When oral prednisolone was combined with local prednisolone 21-phosphate the results were similar to those of local treatment used alone. When oral prednisolone was combined with local hydrocortisone hemisuccinate sodium all the patients so treated showed rapid remission. This second combination therefore emerges as the best of the various treatments studied.

Some practical and theoretical implications of the present results are discussed.

I am grateful to the Medical Research Council for a grant for technical and secretarial expenses in this and other studies on ulcerative colitis. I am also indebted to Glaxo Laboratories, who made a gift of the prednisolone 21-phosphate solution tablets and of much of the hydrocortisone hemisuccinate sodium. I thank the many physicians and surgeons who have referred patients.

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The Catarrhal Child contains the papers read at a symposium held in Glasgow under the chairmanship of Professor Stanley Graham. The symposium, arranged by the Chest and Heart Association in conjunction with the Glasgow Chest Clinic Services, covers, among other aspects of the subject, incidence, bacteriology, and treatment, as well as giving incidental advice on such practical topics as nose-blowing and school attendance. Indeed, its down-to-earth approach to the problem will be of particular value to the general practitioner, who, at least during the winter months, can rarely get through the day without seeing a catarrhal child. (Chest and Heart Association, Tavistock House North, Tavistock Square, London, W.C.1; pp. 44, 6s., illustrated.)

OSTEOMYELITIS OF THE SUPERIOR MAXILLA IN INFANTS

A REPORT ON 24 PERSONALLY TREATED CASES*

BY

FLORENCE CAVANAGH, M.B., B.Sc., F.R.C.S.Ed.
Manchester

In the course of about 100 years there have been reported (so far as I can discover) only 152 cases of this condition. Yet in 17 years I have myself seen and treated 24. This disparity surprised me. Even the more recent reports show some variety in treatment, and the end-results are often unsatisfactory, so that the condition cannot be said to lack interest. It is impossible, in fact, to avoid the suspicion that many cases are not correctly diagnosed. Yet the results of wrong diagnosis and inadequate treatment are by no means negligible. They include sacrifice of teeth, disfiguring scars round the eye, and underdevelopment of the affected maxilla, leading to asymmetry of the face.

I first became interested in this condition in 1940, when I saw a 4-year old boy who had suffered from osteomyelitis of the superior maxilla in the first fortnight of his life. He had scars round his left eye, his face was markedly asymmetrical, as much of the superior maxilla had been removed, and he had no upper teeth on that side. I hoped that when I came to treat one of these babies I should avoid this disfigurement, and it has been most gratifying to find that this is indeed wholly possible if the case is seen at a sufficiently early stage.

Literature

The earliest case in the literature was reported by Rees in 1847. In 1904 Brown Kelly collected 16 records of cases, though 10 of them were entitled "empyema of the antrum of Highmore." In 1922 Marx, an ophthalmologist, discovered 35 recorded cases, and in 1939 Asherson found 70. By 1945 Jacoby and Sagorin had noted 80. I have found a further 72—that is, 152 cases in 111 years.

Most of the papers report isolated cases. Asherson (1939), Reed *et al.* (1953), and Vogt (1956) each reported four cases; Haworth (1947), Schenk (1948), Petrocini and Bullio (1956), and Clerici and Bellina (1957) had five patients each. Dennison (1955), in a paper on osteitis of neonates, mentions eight cases of osteomyelitis of the superior maxilla—occurring over a period of 10 years. Bonnet (1954) saw 15 cases in 20 years, but remarked that this might be due to the fact that he is an ophthalmologist. Incidentally, he reported a mortality rate of 15% in his series.

Clinical Picture

In looking through my case notes and on reading the literature, I was amazed to find how typical most of the histories and findings are; and yet it remains a sad fact that many of these children are treated at eye hospitals as cases of dacryocystitis or are seen by general surgeons who incise the pointing abscess at the outer canthus and never examine the mouth or nose.

The baby with osteomyelitis of the superior maxilla is usually only a few weeks old. Table I shows the age of my patients at the onset of the disease. (It is worth noting that half were under the age of 2 months and 19 out of 24 were under 3 months.)

*Paper read to the Section of Laryngology, the Royal Society of Medicine, London, on December 5, 1958.

The affected baby has usually been quite well until about the day before the doctor is called. He suddenly refuses his food and develops a high temperature. Within 12–24 hours his eyelids have become so oedematous that it may be difficult to see the conjunctiva. There may be chemosis and proptosis. An abscess may be pointing at the inner or outer canthus—or even at the mid-point of the lower eyelid. The cheek is swollen. There is pus in the nostril of the affected side (and none in the other nostril). The alveolus on the affected side is grossly thickened and there is usually a fistula on its outer aspect in the region of the canine fossa or the first deciduous molar. The palate on the affected side is often boggy and bulges downwards, and there may be a palatal fistula. If pressure is applied to the cheek there is an increased flow of pus from the nose or from any of the fistulae.

TABLE I.—*Age at Onset*

< 1 month	8	19	8 months		1
1 ,,	4		19 ,,		1
2–3 months	7		26 ,,		1
6 ,,	1		30 ,,		1

TABLE II.—*Presenting Signs*

Swelling of eyelids	18
,, ,, cheek	13
,, ,, alveolus	14
,, ,, palate	8
Pus in nostril	21
Fistula in alveolus	14
,, ,, palate	6
,, at inner canthus (or abscess pointing there)	2
,, ,, outer canthus (or abscess pointing there)	7
,, in lower lid	3

FIG. 1.—Swollen eye seen in babies with osteomyelitis of the superior maxilla.

We see, therefore, an ill baby with a swollen eye, and it is easy to understand why he is sent to an eye department.

Table II shows the presenting signs in my patients. The two most frequent signs are the swollen eye and pus in the nostril of that side.

Diagnosis and Prognosis

Diagnosis is easy if the condition is borne in mind. When a doctor sees a young baby with one swollen eye he should always examine the nose. If he finds pus in the nostril of the affected side he should look at the alveolus to see whether it is swollen and has a fistula on the outer surface. If he presses gently over the cheek pus will run out of the nose and fistula. The diagnosis is then made without any doubt. These babies are often sent for *x*-ray examination of the maxilla, but personally I have never had any help from such films. Fig. 1 shows the swelling around the eye. Fig. 2 shows the swelling of the hard palate.

The prognosis to-day is excellent. When Asherson (1939) wrote his paper the mortality rate was at least

25%, and Bonnet (1954) gave a rate of 15%. The morbidity rate was much higher. The surviving children continued to have discharging fistulae—on the face, alveolus, or palate. Sequestra were discharged periodically over many years. Some patients developed ectropion—which is a most unsightly condition. Many

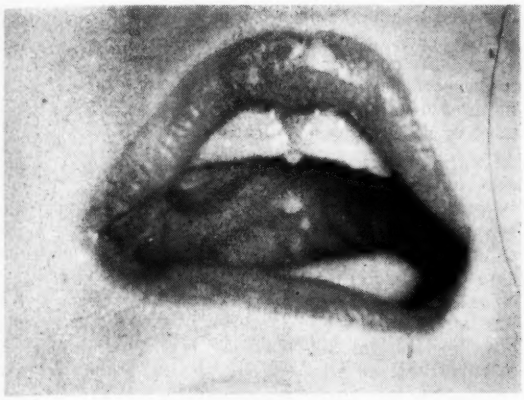

FIG. 2.—Swelling over the hard palate—right side.

had absent or dead teeth on the affected side, and in several children the cheek was reduced in size and the face therefore asymmetrical. To-day these babies stay in hospital for about 10 days, and if diagnosed and treated early there should be no subsequent abnormality —even the milk teeth should be normal.

There has been one death among my 24 patients. This baby came into hospital extremely ill and had a chest infection in addition to the osteomyelitis of the superior maxilla. *X*-ray films of the chest showed several abscess cavities. These ruptured later to give first left and then right pyopneumothorax. The pus from the lung abscess and the pleura contained *Staphylococcus aureus*, as did the pus from the nose.

The Infection

The source of the infection remains obscure. Table III contains the information available in my 24 cases. As the illness often begins in the neonatal period, it has been thought that the child could have picked up the organism in transit through the vagina or perhaps from an abrasion of the gum caused by the midwife's

TABLE III.—*Source of Infection*

Mother	Puerperal pyrexia	1
	Breast abscess	2
Child	Paronychia and infected umbilicus	1
	Large abscess in palm	1
	Styes and boils on cheek	1
Other babies in nursing-home		1

TABLE IV.—*Bacteriology*

Staph. aureus	16
Haemolytic streptococcus	2
Sterile	1
Not recorded	5

cleansing of the mouth at birth. Cracked nipples, breast abscesses, and septic spots on the mother or nurse have all been blamed. In most cases, however, it is impossible to find the cause.

The infecting organism is almost always *Staph. aureus*. This was so in 16 of my 24 cases (Table IV). In one case a haemolytic streptococcus was found in association with *Staph. aureus*. In another case the culture was sterile because the child had had antibiotic treatment before I saw him. In five of my cases the report has been lost or the pus was not sent to the laboratory.

Pathology

The pathology of these cases is still not perfectly clear. Some authors maintain that the lacrimal sac is first affected, others that the maxillary sinus is the original site, and a third group believe that the focus is in the dental sac of the first deciduous molar.

Fig. 3 shows the relationship of the antrum to the dental sac of the first deciduous molar. Figs. 4 and 5 show the antrum in longitudinal section and in horizontal section. Fig. 6 is an *x*-ray picture of the dried neonatal skull, and the antrum is clearly shown.

I am indebted to Mr. Asherson (1939) for the use of these last four illustrations. The dental sac is certainly very large in the neonate, but it is separated by a thick layer of tissue from any superficial abrasion which may have occurred on the gum. Wilensky (1932) claims that the infection is blood-borne. He states that the internal maxillary artery supplies the upper jaw in a series of

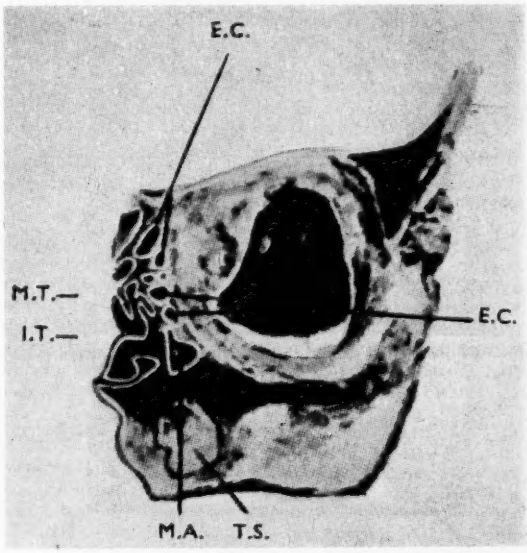

FIG. 3.—Coronal section showing the maxillary antrum (M.A.) and the tooth socket (T.S.) of the first deciduous molar. M.T.= middle turbinal; I.T.=inferior turbinal; E.C.=ethmoid cell.

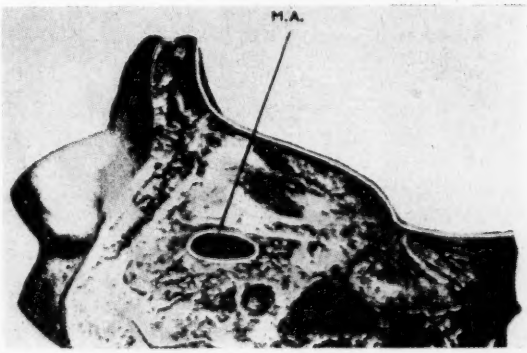

FIG. 4.—Longitudinal section to show the maxillary antrum (M.A.) of the newborn.

loops and that the maximum site of damage depends on which branch carries the infected embolus. The dental sac of the first deciduous molar has a very rich blood supply and would therefore be liable to infection by the blood stream, just as the rich blood supply to the growing end of a long bone determines the site of osteomyelitis.

Poncher and Blayney (1934) and Lederer (1935) discuss the post-mortem findings of one case in which serial sections were taken and the infection was followed over a wide field. They claim that there is "incontestable evidence that the site of entry was the left inferior turbinal" because the lesion of the inferior turbinal was older and more advanced than that in any other part.

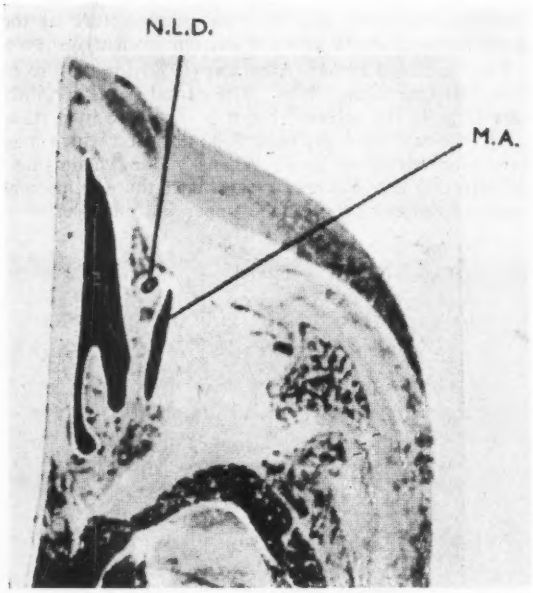

FIG. 5.—Horizontal section showing the maxillary antrum (M.A.) of the newborn. N.L.D. = nasolacrimal duct.

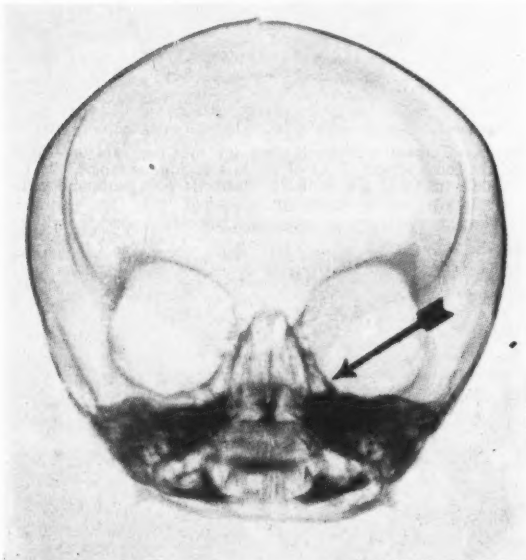

FIG. 6.—*X*-ray picture of a dried neonatal skull to show the maxillary antrum.

Whatever the route by which the infection enters the superior maxilla, we do know that it spreads quickly. The dental sac is certainly infected soon, and in some cases the tooth is forced down by pressure of the pus. It may even be extruded spontaneously. This was described in the older case reports as "premature eruption of the first molar."

FIG. 7.—Forceps passing through the alveolar fistula across the body of the maxilla to appear at the left outer canthus.

The antrum is also involved early — perhaps from rupture of the dental sac into the antrum, or perhaps from the presence of pus already in the nostril. The infection spreads to all surfaces of the maxilla — orbital, facial, alveolar, palatal, nasal — and may spread beyond these parts into the malar bone and the zygoma. If a fistula develops at the inner or outer canthus, a probe passed through it will enter the body of the maxilla. So will a probe passed through an alveolar fistula; and if a third probe is passed through the nose into the antrum it will meet the other two. This central cavity is a fused abscess cavity involving the dental sac, the antrum, and the bone surrounding them.

Fig. 7—taken from Vogt's (1956) paper—shows forceps entering the alveolar fistula and projecting from the one at the outer canthus after traversing the body of the maxilla. D'Arcy Power (1897) had noted that a probe which he inserted at the inner canthus fistula appeared at the fistula in the mouth.

Treatment

It is because this central cavity forms early that treatment via the nose is so effective. The great advantage of draining the abscess through the nose is that it avoids any scar on the face and also avoids any further damage to the teeth. I have never made an incision on the face. Even if the child has an abscess about to point on the face when first seen it has been possible to avoid incision by putting a "polythene" tube through the nostril into the antrum and aspirating the pus twice daily.

Again, I have never used incisions in the alveolus, as I have great regard for the teeth—even the milk teeth, which, after all, hold open the spaces for the permanent teeth. I was horrified to read, in a paper published as late as 1955, that the author had incised the whole length of the alveolus and removed all the dental sacs of the milk teeth.

My own treatment of these infants is now extremely simple. Systemic antibiotic treatment is begun immediately and is continued for 7–10 days. For local treatment, a trocar and cannula is introduced into the

antrum, a polythene tube is then passed down the cannula, and the tube is strapped to the cheek so that the nursing staff can wash out the cavity twice daily with saline and instil the appropriate antibiotic. Pus is aspirated before insertion of the polythene tube—so that the causal organism can be determined as a guide to the antibiotic treatment. The polythene tube remains in position until no pus has been obtained for two or three days; it is then withdrawn.

If the baby should pull out the polythene tube it can be reinserted with very little trouble. If this cannot be done at once, then simple suction applied to the nostril will suffice to withdraw some pus, and this can be repeated several times daily with a minimum of distress.

Illustrative Cases

The following are some points from the case histories of four of my patients.

Case 1

A male infant was first seen in 1944, at the age of 8 months, with osteomyelitis of the right maxilla. Six months previously he had had similar trouble on the left, treated elsewhere. This is the only patient I have had who suffered from the condition on both sides. The original side was still troublesome; sequestra were often removed by his mother from the four fistulae—two on the face, one in the alveolus, and one in the palate. The right side was seen early (three days after the swelling of the eye started), but before we had antibiotics. His antrum was washed out as part of the initial treatment, and it was interesting to see how quickly the right side recovered. He had no fistulae and no sequestration on that side.

FIG. 8.—Case 1. Boy aged 11 with gross thickening of the left upper alveolus and hard palate. The permanent teeth have been affected by the disease.

Fig. 8 shows the gross broadening of the left alveolus and the stumps of discoloured *permanent* teeth at 11 years.

Case 2

A female infant was first seen at the age of five weeks by her general practitioner, who made one incision under the right eye and a second at the outer canthus.

The fistulae continued to discharge, and at 10 weeks she was admitted to hospital. At that time there was an energetic but inexperienced R.S.O., who proceeded to enlarge the fistulae and curette the bone underneath—on three separate occasions. The fistulae continued to discharge and ectropion developed. She was readmitted, and one of the general surgeons excised the scar and removed a sequestrum.

Two months later the fistulae were still discharging, and I was then asked to see the child. She was 15 months old. She had a dirty nasal discharge on the right, and when I examined the alveolus I found an erupting dead tooth. There is no note that the alveolus was looked at previously, though the tongue and pharynx were examined at each admission.

I washed out the antrum, which was full of pus, and put in a Malécot catheter (polythene tubing was not available at that time). After a course of washouts and penicillin instillations, the fistulae on the face closed, and remained closed for some time.

Unfortunately, whenever the child had a cold the infection flared up and the fistulae discharged again. She was admitted for two further periods of antral drainage.

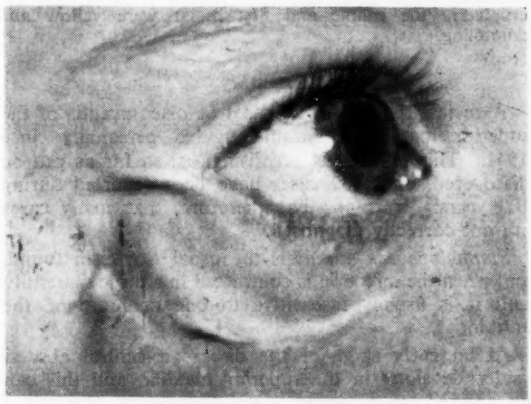

FIG. 9.—Case 2. Skin graft at outer canthus which has corrected an unsightly ectropion. Unfortunately the graft is of different colour from the surrounding skin and is adherent to the underlying bone.

Eventually, when the fistulae had been dry for two years, she was referred to the plastic surgeon for correction of the ectropion. She has now had a free graft and the unsightly ectropion has been corrected, but the graft is different in colour from the surrounding skin and is adherent to the bone. A further plastic operation will be carried out later, but I think the child will always have some disfigurement. Fig. 9 shows the appearance at present.

Case 3

This boy was desperately ill when first seen as a baby and had had only systemic antibiotic treatment. He is of special interest because he developed osteomyelitis of the left humerus on the second day after admission—the only complication of this type that I have seen. (In the literature, however, Posey (1912) reports a case in which osteomyelitis of the tibia developed; and White (1935) records the case of a patient who had secondary osteomyelitis of the humerus. Gregson and Yeoman (1957) saw a patient who developed osteomyelitis of the calcaneus.)

Four of the milk teeth in the left upper jaw were affected. They were small and yellow, and soon crumbled away to mere stumps. Fig. 10,

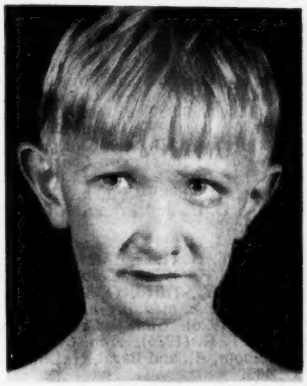

FIG. 10.—Case 3. Showing asymmetry of the face following osteomyelitis of the left superior maxilla.

taken at the age of 6, shows the marked asymmetry of the face—resulting from destruction of much of the left superior maxilla.

Case 4

A male infant had severe involvement of the teeth. He was admitted to an outside hospital when 2 weeks old and a tooth bud was removed. He was readmitted three weeks later and a further tooth was removed. After that, various small sequestra were picked out by his mother.

The child was nearly 5 months old when I first saw him; he then had a large swelling over the outer and upper part of the cheek. There was pus in the nose and in the alveolar fistula. The central and lateral incisor teeth never erupted; the canine and first molar were yellow and crumbling.

Summary

A review is given of 24 cases of osteomyelitis of the superior maxilla in infants treated personally since 1941. This number is surprising, as, so far as can be discovered, only 152 cases have been reported during 100 years. It is possible, therefore, that many cases are not correctly diagnosed.

Staphylococcus aureus is the usual organism found, and when the infection is contracted in a large maternity unit it is usually insensitive to one or more of the antibiotics.

At an early stage of the disease a central abscess cavity develops in the superior maxilla, and this can be drained by inserting a polythene tube through a cannula which has punctured the lateral nasal wall under the inferior turbinal. By this means antibiotics can be instilled locally. The baby is also given systemic antibiotics.

No incision should be made in the alveolus, or the teeth will be further damaged and incisions around the eyes should be avoided, thus preventing unsightly scars.

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"I would like to express once again the hope that young West African scientists in ever-increasing numbers may be attracted to the field of medical research. There is a feeling that research workers are oddities. Perhaps there are a few—you can't do without some of them. Some three or four years ago on my arrival in Dar-es-Salaam a medical administrator who met me remarked after an awkward silence, 'You know, you people are a race apart. You're quite different from other people.' Later, when I was sounding a very experienced medical administrator in East Africa as to whether he would be willing to become Secretary of our East African Council for Medical Research, he commented, 'But surely you want one of those young men with beards and sandals.' It is true that we have our prima donnas, but we have no monopoly of them; there must be many in other vocations than medical research. It is true that we have to include the peculiar and the unorthodox, because very often they have something of vital importance to contribute. But, taken by and large, the stigmata of the medical research worker can be summed up, as I have already mentioned, in the fact that he is imbued with the simple worth-whileness of finding out why something happens, and with the zeal to pursue that quest." (Dr. R. Lewthwaite, Presidential Address, Conference on Tuberculosis and Leprosy, Northern Nigeria.)

RESPONSE OF THE CONJUNCTIVAL VESSELS OF DIABETICS TO "PRISCOL"

BY

HARRY KEEN, M.B., M.R.C.P.*
Research Fellow, Medical Unit, St. Mary's Hospital, London

AND

REDMOND SMITH, M.S., F.R.C.S.†
Consultant in Ophthalmology, St. Mary's Hospital, London

The accessibility of the human conjunctiva to direct examination has led many workers to study the structure and behaviour of its vessels in life (Graves, 1934; Lack *et al.*, 1949; Ditzel and Sagild, 1954). Not unreasonably, it has been suggested that certain general vascular abnormalities might reveal themselves in disordered structure or function at this site. The present study was based upon such a suggestion made by N. Ashton and C. A. G. Cook (1954, personal communication); they suspected, from clinical observations, that the conjunctival vasodilatation caused by "priscol" (tolazoline hydrochloride) eye drops was much less conspicuous in diabetics with retinopathy than in diabetics with normal fundi. These observations suggested to them the possibility of a circulating vasoconstrictor substance influencing the conjunctival vessels of the patients with retinopathy and, perhaps, also responsible for constriction of the pre-capillary arterioles of the retina with stasis and micro-aneurysm formation distally (Ashton, 1953).

We tested the reality of the clinical impression when the opportunity arose to examine a large number of eyes in an extensive study of diabetic retinopathy.

Method

Priscol, probably acting directly upon the vessel wall (Goodman and Gilman, 1955), causes striking reddening of the normal eye when strong solutions are put into the conjunctival sac (Fig. 1). Two concentrations of the drug, 1/500 and 1/650 in sterile distilled water, were selected by a trial-and-error method as being adequate to produce conjunctival vasodilatation in most but not all normal eyes and thus likely to display a variation in response in the patients. Distilled water alone produced no appreciable vascular effect at five minutes.

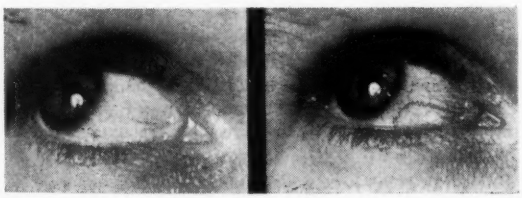

FIG. 1.—The conjunctival vessels before and 5 minutes after instilling priscol.

Both eyes of 297 patients of the Diabetic Clinic at St. Mary's Hospital were studied. Table I shows the age and sex composition of the group. Each patient's eyes were first examined with the slit-lamp and corneal microscope, and those with corneal or conjunctival disease were excluded. These exclusions, inadequate record, and occasional patients with an eye removed, account for the small disparities between the number of patients in the group and the total number of eyes examined. One drop of the 1/500 priscol solution was then placed in one eye, usually the right, and one drop of the 1/650 solution in the other. The eyes were again inspected after a lapse of five minutes and the degree of reddening in each was recorded on an arbitrary scale of from nil to three plus (0, +, ++, +++). Throughout the study, the instilling of drops and the reading of the response were done by the same observer (R.S.), who, later, also inspected the fundi.

TABLE I.—*Age and Sex of Diabetics Examined*

	20–	30–	40–	50–	60–	70–	Total
Male	5	16	22	25	27	12	107
Female	16	10	17	47	64	36	190
Total	21	26	39	72	91	48	297

TABLE II.—*Comparison of Responses at the Two Concentrations*

		0	+	++	+++	Total	Mean Response
1/500	No. ..	18	89	106	82	295	1·854
	% ..	6·1	30·2	35·9	27·8	100	
1/650	No. ..	33	101	98	46	278	1·565
	% ..	11·9	36·4	35·2	16·5	100	

$\chi^2 = 15{\cdot}049$. n = 3. $P < 0{\cdot}01 > 0{\cdot}001$.

Comparison of the Two Concentrations

Table II shows the incidence of the various grades of response at the two concentrations. If these arbitrary grades are treated numerically by making each plus value count one, the mean response at the higher concentration is 1.854, a value significantly greater than that at the lower concentration, 1.565 ($p<0.01$). Comparison of the distribution of responses at the two concentrations also demonstrates a highly significant difference between them ($\chi^2=15.049$, $p<0.01$).

Influence of Age and Sex upon Response

A clear relationship between the age and sex of the subject and the response to priscol can be seen in Fig. 2, in which the mean priscol responses for each 10-year age group, calculated separately for men and women (Table III), have been plotted. The response increases with age, and is greater in males than in females at all ages. The straight lines represent the calculated regression of response upon age; the degree of correlation between the two factors, though small, is significant in both sexes at the 1/500 concentration (men: $r=0.240$, $p<0.05$; women: $r=0.368$, $p<0.05$). At the 1/650 concentration, as expected, the mean values of response are, age for age, lower

TABLE III.—*Priscol Response (Means) by Age and Sex*

		20–	30–	40–	50–	60–	70–	r	p
1/500	M. ..	1·33	1·75	1·68	2·16	2·18	2·18	0·240	<0·05
	F. ..	0·85	1·30	1·47	1·89	1·92	2·12	0·368	<0·05
	All	0·94	1·58	1·59	1·99	2·00	2·13		
1/650	M. ..	0·67	1·80	1·40	2·05	1·92	1·91	0·202	<0·1
	F. ..	0·69	1·13	0·88	1·59	1·58	1·73	0·237	<0·05
	All ..	0·67	1·56	1·16	1·74	1·68	1·77		

*Work done partly during tenure of a Lund Research Fellowship of the British Diabetic Association.

†Work done during the tenure of a Moorfields Research Fellowship, in the Department of Pathology, the Institute of Ophthalmology, London.

than at 1/500 (Table III); the sex difference and the increase with age are shown in Fig. 3. The correlation between response and age, though significant in the women, just fails to achieve significance at the 1 in 20 level in the men (men: $r=0.202$, $p<0.1$; women: $r=0.237$, $p<0.05$).

Further Analysis of the Age-response Relationship

The correlation with age is a statistical phenomenon only, casting no direct light upon the precise biological mechanism determining the change. We sought further leads by examining the priscol response in relation to two characteristics, themselves related to age—namely, the duration of the diabetes and the arterial blood pressure.

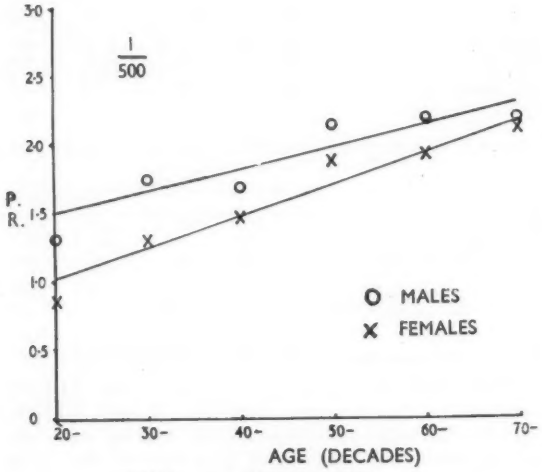

FIG. 2.—Response to 1/500 concentration of priscol in relation to age and sex.

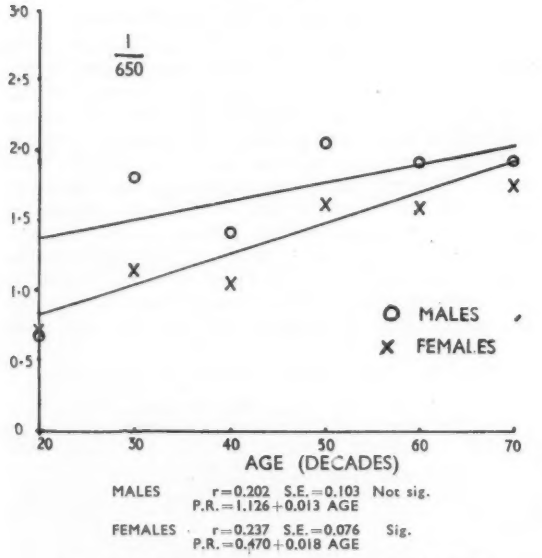

FIG. 3.—Response to 1/650 concentration of priscol.

TABLE IV.—*Priscol Response (Means) by Duration of Diabetes*

		0–	5–	10–	15–	20–	25+	Total
1/500	No.	176	53	27	24	10	5	
	Mean response	1·90	1·81	1·67	2·00	1·70	1·20	295
1/650	No.	169	47	24	24	10	4	
	Mean response	1·61	1·42	1·54	1·79	1·30	0·75	278

Influence of Duration of Diabetes.—In Table IV, the mean priscol responses are shown for each five-year duration group. The relationship between these two factors is poor, and statistically is not significant (1/500 $r=0.039$; 1/650 $r=0.015$).

Influence of Blood-pressure.—Since Hamilton *et al.* (1954a) have shown that arterial blood-pressure rises with age, a correlation between the priscol response and the blood-pressure might be expected simply on the basis of a common effect of age upon both. Age is not the only factor that influences the blood-pressure, for a considerable variation in pressures about the mean is found at all ages (Hamilton *et al.*, 1954a). Though in order to seek a relationship between pressure and priscol response independently of the effects of age it might at first sight appear necessary to examine each age group separately, it is possible to make suitable statistical adjustment to pressures, so as to remove only that part of the variation due to the effect of sex and age; correlations with the residual variation can then be sought. We have used the method of adjustment and the tables of Hamilton *et al.* (1954b) and calculated age-and-sex-adjusted blood-pressure score for each patient; the score represents the deviation of an individual pressure from its sex- and age-group mean, adjusted with regard to the increasing variation of blood-pressure with age to a corresponding deviation at 60 years of age.

When these scores, systolic and diastolic, were studied in relation to the priscol responses, no significant correlation between the two was found.

	1/500	1/650
Systolic	... $r=0.059$	... $r=-0.016$
Diastolic	... $r=-0.045$	... $r=0.026$

Influence of Retinopathy upon Priscol Response

In order to examine the original contention of a lessened response to priscol in diabetics with retinopathy, patients with cataract were excluded from the analysis and the remainder divided into four groups on the basis of the appearance of the fundi. Group 1 patients had no micro-aneurysms (defined as discrete red dots); group 2 had up to 5; group 3 had 6 to 10; group 4 had more than 10. The distribution of the various grades of priscol response in these retinopathy groups is shown in Table V; the results of the χ^2

TABLE V.—*Priscol Response and Retinopathy*

Retinopathy Group	1/500 Priscol Response					1/650 Priscol Response				
	0	+	++	+++	Total	0	+	++	+++	Total
1	10	56	62	52	180	19	65	56	33	173
2	1	14	24	12	51	2	15	23	5	45
3	2	5	9	4	20	4	6	6	3	19
4	5	10	7	5	27	6	11	8	1	26
Total	18	85	102	73	278	31	97	93	42	263

$\chi^2=13{\cdot}50$. $n=9$. $P=<0{\cdot}2>0{\cdot}1$. $\chi^2=15{\cdot}38$. $n=9$. $P=<0{\cdot}1>0{\cdot}05$.

analyses indicate the absence of a relationship between the two factors. This is confirmed by the results shown in Table VI, where it can be seen that the proportion of poor priscol responses (0 and +) was the same whether retinopathy was present or not.

TABLE VI.—*Priscol Response and Retinopathy*

Retinopathy	1 500 Priscol Response		1 650 Priscol Response	
	Weak	Strong	Weak	Strong
Absent	36·6%	63·4%	48·5%	51·5%
Present	37·8%	62·2%	48·9%	51·1%

Discussion

The effects of priscol upon the blood vessels of diabetic patients have been studied by many workers; evidence for impairment of priscol-induced vasodilatation has been demonstrated in the feet by Handelsman *et al.* (1952) and in the retinal vessels by Cholst *et al.* (1952).

Several factors may influence the intensity of the effect of a priscol solution upon the conjunctival vessels, including the concentration of the substance, its penetration through the conjunctival epithelium, the responsiveness of the vessel wall, and the rate of destruction, dilution, and removal from the eye. Comparison of the effects of the 1/500 with the 1/650 concentration show that quite small differences in strength produce a perceptible difference in effect; this finding, however, would be considered better established if the eyes had been assessed quite independently of each other.

The sex difference and the age trend in response can, however, be accepted with confidence, especially since they were completely unforeseen and emerged only at the final analysis of results. It has been shown that duration of the diabetes and the level of arterial blood-pressure are unrelated to these trends. We also failed to find evidence that the response was in any way influenced by the presence of diabetic retinopathy, an observation in accord with that of Bárány (1955), who found no greater diminution of heat elimination from the skin blood vessels of diabetics with retinopathy than from those without it. Cholst *et al.* (1952), however, claimed that, when retinopathy was present, priscol did not produce normal retinal vasodilatation, which they assessed by the increase in width of the scotoma cast upon the visual fields by the retinal vessels.

A possible explanation of our findings may lie in de Roetth's (1953) investigations into the influence of age and sex upon the rate of tear production. Fig. 4, which is derived from his data, shows the mean rate of tear production in 10-year age-groups for normal men and women. Tear production was estimated by the method of Schirmer (1903), measuring the wetted length of a filter-paper strip of standard width five minutes after insertion into the lower conjunctival fornix. The figure shows a clear tendency for tear production to decrease with age, and, at most ages, to be less in men than in women. Assuming that sex and age exert a similar influence upon the rate of tear production in the diabetic, de Roetth's results suggest the simplest explanation for our findings; for the higher the tear flow, the more effective would be the dilution and washing out of priscol. This would account both for the lower priscol response in women, and the increase in response with age. The most intense response to priscol vasodilatation which we saw was in a middle-aged woman with kerato-conjunctivitis sicca who was excluded from the analysis because of this condition.

If, in fact, the increase of effect with age is due to the decline in tear production, then the practical implications may be wide: a similar influence may affect other substances placed in the conjunctival sac for diagnostic, therapeutic, and experimental purposes. It may, for example, partly explain the widely accepted clinical observation that the mydriatic and cycloplegic drugs used locally in diagnostic procedures act less efficiently in the young than in the old. The employment of a local analgesic to potentiate the action of such drugs may well owe its effect not only to the synergic action and an increase in corneal permeability, but also, as demonstrated by Schirmer (1903), to inhibition of the lacrimatory reflex. The ophthalmoreaction of Calmette (1907), provoked by instilling tuberculin into the eye, enjoyed a brief vogue as a diagnostic test for

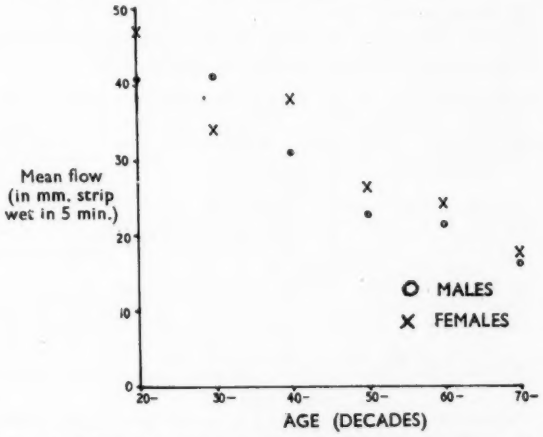

FIG. 4.—Mean rate of tear production in 10-year age groups of normal subjects. (From de Roetth's data.)

tuberculosis; its abandonment was due not only to the occasional unpleasant sequels in the eye but also to the lack of reliability of the response; one astute observer ascribed his negative results in children to the possibility that "tears washed out the testing fluid" (Woodcock, 1908).

Therapeutically, the findings would seem to indicate the need to consider age and sex in relation to the frequency of application and the concentration of eye-drops. Furthermore, while in the young the effects of drugs upon the eye may be lessened by the greater tear-flow, the systemic effects may be correspondingly enhanced by more rapid alimentary absorption.

Variation in tear production is clearly of importance in the interpretation of experimental studies upon the conjunctival response to drugs. Ridley (1932) timed the disappearance of coloured solutions of differing concentration from the eye, and hence calculated the rate of tear production. His general conclusions display no awareness of variation with age and sex. Where the effects of two substances are being compared, or when an agent is being compared in two groups of people, false conclusions may readily be drawn if the sex and age of the subjects are not considered. Lee and Holze (1950, 1951) examined the response of the conjunctival vessels to locally applied adrenaline, and claimed that

the vasoconstriction which it produced was greater in patients with essential hypertension than in normal controls. Their controls, however, were healthy *young* subjects whose relative lack of response may thus quite possibly have been due merely to greater dilution and washing out of the adrenaline by tears.

Conclusions

The vascular response of the conjunctiva to locally instilled priscol has been recorded in 297 diabetics.

Analysis shows a significant correlation between this response and the concentration of the drug, and also with sex and age.

There was no relationship between the response and the adjusted blood-pressure score, the duration of diabetes, or the presence of retinal micro-aneurysms.

This variation of the response with age and sex may be related to the rate of tear production, which, in normals, has been shown to be greater in females and to decrease with age.

The diagnostic, therapeutic, and experimental implications of these findings are considered.

We thank Dr. C. A. Young, physician in charge of the diabetic clinic, St. Mary's Hospital, and the photographic departments of St. Mary's Hospital and the Institute of Ophthalmology.

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"It is this matter of 'communication' which lies at the root of the National Council of Social Service's work; and assumes a greater importance as the machinery of the Welfare State is elaborated and its philosophy is developed. For there seems to be opposition between these two things. Each year sees additions to the already complicated structure which the State is erecting for welfare, education, health, and so on; and with every new job, defined in terms of duties and responsibilities over against a pre-existing job, the problem of communication is increased by the erection of new invisible boundaries. Yet the philosophy which seems at the same time to guide all present-day social thinking is based on the need for coming together, for community responsibility, for bringing our social misfits out of their specialized institutions into the everyday world. The whole structure of the National Council was designed to make easier this communication between the national voluntary organizations among themselves and with the statutory bodies, both at the centre and, by means of local groups, throughout the country. Some of the ways in which the Council's departments and associated groups have, in their different but interdependent fields, worked towards that purpose during the past year are shown in this year's report." (*40th Annual Report*, National Council of Social Service.)

PROTEINS OF THE LIQUOR AMNII

BY

T. M. ABBAS, M.D., F.R.C.S.Ed., M.R.C.O.G.
Lecturer in Obstetrics and Gynaecology, University of Bristol

AND

J. E. TOVEY, M.B., Ch.B.
Registrar, Department of Pathology, Southmead Hospital, Bristol

Despite all the available information concerning the composition, origin, and fate of the liquor amnii, our knowledge with regard to this fluid remains incomplete. This communication presents an evaluation of the results obtained with paper electrophoresis of the protein pattern in the amniotic fluid, maternal serum, umbilical cord blood, and *in vitro* dialysates. The study was primarily undertaken for the purpose of obtaining further data on the possible source, nature, and function of the protein in the liquor amnii. It was also hoped that it might elucidate certain important and related clinical problems, such as the nutritional value of the swallowed liquor to the foetus and the possible diagnostic value of any detectable atypical electrophoretic pattern in abnormal pregnancies.

A review of the meagre literature on electrophoresis of the liquor (McCarthy and Kekwick, 1949; Bramwell *et al.*, 1953; Candiani, 1956; Wirtschafter and Williams, 1957a, 1957b; McKay *et al.*, 1958) shows that much of this work has been done on experimental animals. These studies have yielded some interesting information. For instance, in rats Wirtschafter and Williams (1957a, 1957b) have shown that in contrast to the maternal serum the albumin/globulin ratio in the liquor of these animals is subject to characteristic fluctuations. High albumin readings were noted at parturition in normal cases and a correspondingly high globulin value in abnormal ones. Brambell *et al.* (1953), on the other hand, reported that β- and γ-globulin in immune rabbit serum enter foetal circulation when such a serum is injected into the pregnant uterine lumen. The clinical significance of such findings, if observed in the human, could be of inestimable value, but the only two available studies on the liquor in man (Candiani, 1956; McKay *et al.*, 1958) have been controversial and not entirely in agreement with one another. In view of this, and because of the primary role of protein in foetal metabolism, it was felt that a further study in this field might prove instructive.

Material and Method

Samples of liquor amnii and venous blood were collected from 11 essentially normal patients who were surgically induced at 40 weeks plus five days. To avoid contamination all samples of amniotic fluid were withdrawn from the hind-water with a Drew Smythe catheter.

In seven additional cases enough maternal blood was removed to provide an adequate quantity of serum for *in vitro* dialysis against normal saline across their respective "foetal" membranes. The membranes utilized in the dialysis were in each case selected from an area about $\frac{1}{2}$ in. (1.3 cm.) beyond the placental edge. Care was also taken to ensure that each specimen included both amniotic and chorionic layers. The electrophoretic findings in the resultant saline dialysate

were in each case compared with that of the original liquor aspirated from the same patient.

Electrophoretic studies were also conducted on liquor collected from five cases of severe pre-eclampsia, three cases of anencephaly with hydramnios, two cases of hydramnios with no demonstrable underlying abnormality, one case of uniovular twins with hydramnios, and another case of Rh incompatibility with hydrops foetalis. In addition the protein-distribution curves of samples of cord blood removed at delivery from most of the cases in this study, including that from a baby with oesophageal atresia, were similarly analysed.

The electrophoretic technique adopted for this study entailed the use of the inverted V apparatus, as described by Flynn and de Mayo (1951), a barbitone buffer (0.515 g. of sodium diethylbarbitone, 0.092 g. of diethylbarbituric acid, and 0.415 g. of sodium caprylate made up to 100 ml. with distilled water), and Whatman No. 1 filter-paper. Each electrophoretic strip was run in the apparatus for 18 hours at 150 volts, then dried at room temperature and stained with azocarmine B (Gurr). These stained strips were interpreted by the reflecting photodensitometer (Latner *et al.*, 1954), and all recordings finally corrected for non-linearity between the amount of dye present and the amount of protein.

Prior to each electrophoretic run the total protein content of the liquor amnii was estimated by the method of Denis and Ayer (1920), and in order to obtain readable patterns each sample was concentrated by dialysis through a Viskap membrane against 25% solution of polyvinylpyrrolidone made up in electrophoretic buffer.

To ensure accuracy, all electrophoretic tests in this study were duplicated.

Results

The mean total protein content of the amniotic fluid in the 11 five-days-postmature but otherwise normal cases varied from 160 to 285 mg., averaging 210 mg./100 ml. These results are comparable with the findings of Zangemeister (1908) and Makepeace *et al.* (1931), but they fall short of the values obtained by Taussig (1927), Cantarow *et al.* (1933), and McKay *et al.* (1958).

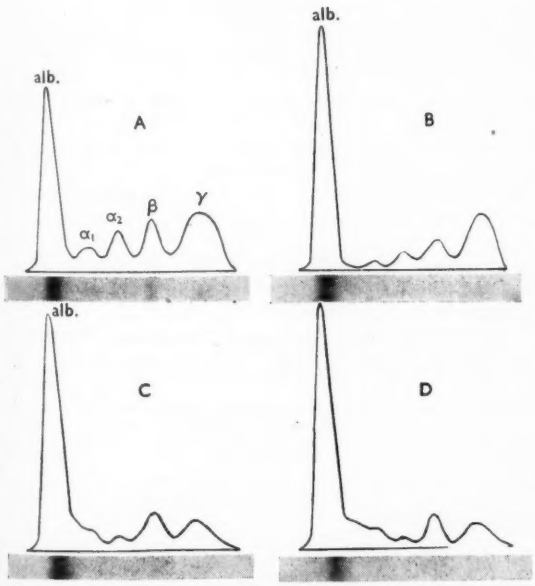

FIG. 1.—Electrophoretic protein pattern and distribution curves as seen in (A) maternal blood, (B) foetal cord blood, (C) liquor amnii, and (D) maternal serum dialysate.

TABLE I.—*Mean Values of Protein Fractions in Maternal Sera, Liquor Amnii, and Cord Blood Collected from 11 Normal Patients*

	Alb.	α_1	α_2	β	γ	Total Protein (g./100 ml.)
Maternal serum	54·4 (±4·5)	4·9 (±0·7)	10·0 (±1·4)	15·8 (±1·7)	14·9 (±3·6)	6·6
Liquor ..	68·6 (±7·6)	6·2 (±1·3)	4·6 (±2·2)	11·7 (±3·7)	8·9 (±2·8)	0·21
Cord blood ..	67·7 (±3·2)	3·0 (±1·0)	5·7 (±2·2)	7·3 (±2·4)	16·3 (±3·1)	5·4

Units = percentage of dye present. S.D. (n − 1) given in parentheses.

TABLE II.—*Comparison of the Mean Electrophoretic Results of Liquor Amnii and Dialysates in 7 Cases*

	Alb.	α_1	α_2	β	γ
Liquor amnii ..	67·0 (±5·1)	6·1 (±1·3)	5·6 (±1·9)	13·9 (±1·8)	7·4 (±2·0)
Dialysate ..	67·5 (±5·2)	6·0 (±1·3)	5·1 (±1·9)	14·6 (±2·8)	6·8 (±1·8)
P	0·8	0·9	0·6	0·6	0·6

Units = percentage of dye present. S.D. (n − 1) given in parentheses. P = probability (Fisher's "t" test).

TABLE III.—*Electrophoretic Patterns Seen in the Liquor Amnii in Certain Types of Abnormal Pregnancies*

	No. of Cases	Alb.	α_1	α_2	β	γ	Total Protein (g./100 ml.)
Normal pregnancy	11	68·6 (±7·6)	6·2 (±1·3)	4·6 (±2·2)	11·7 (±3·7)	8·9 (±2·8)	0·21
P.E.T.	5	63·2	9·0	5·7	12·7	9·4	0·23
Anencephaly with hydramnios	3	71·4	6·4	3·4	11·1	7·7	0·4
Hydramnios (with no other abnormality)	2	66·6	6·8	4·8	13·7	8·1	0·31
Twins with hydramnios	1 (a)*	71·2	7·1	6·2	8·6	6·9	0·22
	1 (b)	70·6	9·4	5·8	8·4	5·8	0·22
Rh—incompatability. Hydrops foetalis	1	69·3	3·4	6·0	11·5	9·8	0·3

Units = percentage of dye present. S.D. (n − 1) given in parentheses.
* From amniotic sac with hydramnios.

Fig. 1, A shows that maternal serum protein can be electrophoretically separated into five major fractions, digressing on the test strip according to their mobility in the following order—albumin followed by α_1-, α_2-, β-, and γ-globulin. Representative examples of electrophoretic protein patterns, as seen in foetal blood, liquor amnii, and maternal serum dialysate are also shown in Fig. 1.

Table I demonstrates the mean values for protein fractions in maternal sera, liquor amnii, and cord blood collected from 11 normal parturients.

Table II represents the mean electrophoretic results of seven samples of liquor amnii and of their corresponding number of dialysates obtained from maternal sera across their respective foetal membranes. It is interesting to observe the close similarity of these two groups of figures.

Table III shows the mean protein values in the liquor amnii in the five cases of severe pre-eclampsia, three cases of anencephaly with hydramnios, two cases of hydramnios with no demonstrable underlying abnormality, one case of uniovular twins with hydramnios, and one case of Rh incompatibility with hydrops foetalis.

Discussion

The technique of paper electrophoresis has provided a new approach to the study of protein in different body

fluids. The present investigation was designed to utilize this procedure to supplement our knowledge on the protein of the human liquor. The initial findings disclosed certain interesting features which induced us to extend the study, and this in turn led to several attractive observations.

The first of these observations concerns the findings in the liquor of a protein pattern suggestive of a serum dialysate. This feature was repeatedly seen on comparing electrophoretic results of the liquor amnii with that of the corresponding maternal serum. Table IV illustrates

TABLE IV.—*Electrophoretic Results of Liquor Amnii and the Corresponding Maternal Serum*

	Alb.	α_1	α_2	β	γ
Maternal serum	54·4	5·8	12·4	16·3	11·1
Liquor amnii ..	65·5	6·8	6·1	14·2	7·4

Units = percentage of dye present.

a typical example. The "small" albumin molecule with a weight of 69,000 appeared in the liquor in a relative concentration of 65.5% against 54.4% in maternal serum, while α_2 globulin with the most consistently high molecular weight of 300,000 showed a relative concentration of 6.1% in the liquor as against 12.4% in maternal serum. Similarly, the relative values of α_1-, β-, and γ-globulin in the two fluids represented a comparable relationship which was apparently determined by the "size," and therefore the ease with which the different protein molecules can traverse a barrier such as the trophoblastic membrane. To provide further evidence in support of this hypothesis we dialysed maternal sera across the corresponding foetal membranes, and in each case the resultant dialysate pattern was found to be similar to that seen in the original liquor. To obviate any possible secretory mechanism the membrane in each of the seven *in vitro* tests carried out for this purpose was placed in such a manner that the foetal surface was positioned next to maternal serum. Other subsequent experiments showed that it did not matter which way the membrane was placed between the two fluids.

The result of one of these experiments is given in full detail in Table V, demonstrating the close similarities between the protein pattern of the liquor amnii and that

TABLE V.—*Electrophoretic Protein Pattern in Maternal Serum, Liquor Amnii, and Saline Dialysate of Maternal Serum Across Foetal Membranes*

	Alb.	α_1	α_2	β	γ
Serum ..	55·7	4·0	11·4	15·0	13·9
Liquor amnii ..	72·0	3·5	4·4	11·9	8·2
In vitro dialysate	73·5	3·7	3·8	11·2	7·8

Units = percentage of dye present.

seen in the corresponding *in vitro* saline dialysate. The albumin content of the liquor was 72% against 73.5% in the dialysate, and the values for α_1-, α_2-, β-, and γ-globulin were 3.5, 4.4, 11.9, and 8.2 as against 3.7, 3.8, 11.2, and 7.8 in the liquor and the dialysate, respectively. Minor differences in these figures are well within the errors of the electrophoretic method.

According to these results one may reasonably conclude that the protein of the liquor is derived from maternal blood across the whole of the "foetal" membranes, which lie virtually in direct contact with the whole of the vascular uterine mucosa.

The second interesting observation concerned the probable nutritional value to the foetus of the swallowed protein of the liquor amnii, especially during the later weeks of intrauterine life, when the functional capacity of the foetal alimentary tract is adequate and the placental efficiency is on the wane.

The difficulties and limitations of any inquiry about intrauterine nutrition are self-evident, but two lines of investigation in this respect proved helpful: (1) the finding of a subnormal standard of birth weight in babies born with congenital oesophageal atresia as shown in a group of 47 cases illustrated in the scattergram (Fig. 2); and (2) the demonstration of a low γ-globulin value in the cord blood of two infants born with this deformity (Table VI). No doubt the interpretation of these findings is open to several possibilities, but the teleological significance appears to suggest that the ability of the foetus to swallow and assimilate liquor amnii can influence its birth weight and possibly its serum γ-globulin level. This latter speculation is of special interest when one considers that the transmission of antibodies in man can occur from maternal circulation to the foetus either through the placenta and the vascular

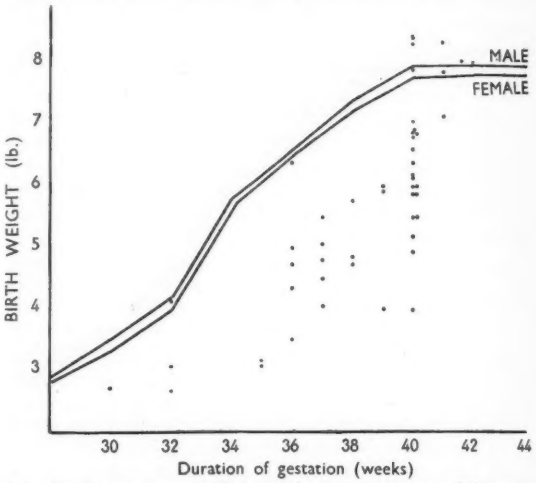

FIG. 2.—Scattergram of birth weights and maturity of 47 cases of oesophageal atresia plotted against a normal birth-weight curve (Gibson and McKeown, 1952).

route or via the chorion laeve into the amniotic fluid and foetal gut. Brambell *et al.* (1947) have shown that, in the rabbit, "transfer of antibodies occurs by way of uterine lumen into the amniotic fluid and foetal stomach and not via the placenta." They also reported (Bramwell *et al.*, 1951, 1954) that antibodies are absorbed in quantity from "the gut contents of newborn ruminants, horses, pigs, dogs, mice, and rats." It would be in keeping with these findings to record that the same route of transmission occurs in man.

The third observation is concerned with the evaluation of atypical electrophoretic liquor patterns and its

TABLE VI.—*Electrophoretic Record of Cord Blood in Two Cases of Oesophageal Atresia*

		alb.	α_1	α_2	β	γ	Total Protein (g.)
Oesophageal atresia	(1)	73·8%	4·1	6·6	7·9	7·6	5·6
	(2)	76·1	2·2	4·9	9·3	7·5	6·0
Normal record		67·7 (±3·2)	3·0 (±1·0)	5·7 (±2·2)	7·3 (±2·4)	16·3 (±3·1)	5·4

Units = percentage of dye present. S.D. (n − 1) given in parentheses.

possible diagnostic import. Despite the limited number of abnormal cases studied (Table III), the results show only minor variations from the normal which could be explained on the grounds of changes in maternal serum proteins; for instance, the low value of serum albumin in toxaemia may well be responsible for the correspondingly low albumin reading in the liquor, and this may also apply to the high α_1-globulin levels in the liquor of these patients.

The significance of the slightly elevated total protein in the liquor in anencephaly, hydramnios, and hydrops foetalis, and its possible relationship to foetal swallowing, can only be a matter of conjecture. On the other hand, the findings of identical protein patterns in the two amniotic sacs of uniovular twins where hydramnios was limited to the upper of the two sacs, as confirmed on abdominal paracentesis, shows that there is more to it than foetal swallowing, and protein dialysis in the complex processes involved in the formation and elimination of all the constituents of the amniotic fluid.

Summary

Proteins present in maternal serum, umbilical-cord blood, liquor amnii, and dialysates from maternal serum across "foetal membranes" have been studied with the aid of paper electrophoresis.

The protein pattern seen in the liquor amnii has the characteristics of a simple protein dialysate, and can be reproduced *in vitro*.

Evidence is presented to suggest that the swallowed liquor amnii contributes to foetal nutrition and may well provide a source of γ-globulin and antibodies to the foetus.

Despite minor variations, no diagnostically significant changes were detected in the electrophoretic patterns of the liquor in toxaemia, anencephaly, twins, hydramnios, and hydrops foetalis.

We particularly wish to thank Dr. F. J. W. Lewis, director of pathology, Southmead Hospital, for his advice and criticism, and for the co-operation of his department. We are grateful to Professor G. G. Lennon for his interest and encouragement. We are indebted to Mr. R. H. R. Belsey, Frenchay Hospital, and Dr. N. J. Brown, Southmead Hospital, for permission to study their records of oesophageal atresia.

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DEMONSTRABLE DEFICIENCY OF CHRISTMAS FACTOR IN TWO SISTERS

BY

I. A. COOK, M.D.

Department of Pathology, Southern General Hospital, Glasgow

AND

A. S. DOUGLAS, M.D., B.Sc., F.R.C.P.Ed. F.R.F.P.S., M.R.C.P.

University Department of Medicine, Royal Infirmary, Glasgow

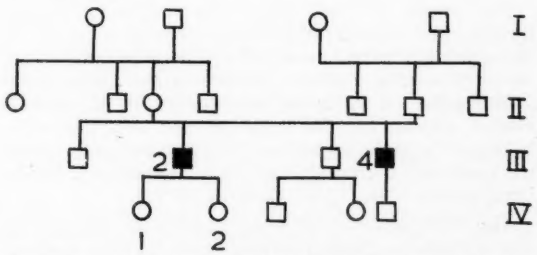
Evidence indicates that Christmas disease is inherited as a sex-linked recessive defect. This was suggested by one of the family trees in the first seven cases of Christmas disease reported by Biggs *et al.* (1952). Numerous family trees published since that time have confirmed this. Koller (1954), for example, demonstrated that four members of the famous Tenna family of bleeders in Switzerland, where the inheritance is of this pattern, are affected with Christmas disease.

In a genetic defect of this type the disease is transmitted by apparently normal carrier females to an affected male. All the daughters of an affected man are carriers. In the family of a carrier there is a 50% chance of a daughter being a carrier and of a son being affected. Biggs *et al.* (1952) noted a prolonged clotting-time and defective prothrombin consumption in the mother of one of their cases. Brinkhous *et al.* (1954) reported P.T.C. (Christmas factor) deficiency in a woman aged 49. Such cases suggested that the Christmas-disease gene might be less completely recessive than that producing haemophilia (Pitney and Dacie, 1955).

The object of the present paper is to record a demonstrable deficiency of Christmas factor in two sisters, the daughters of a man suffering from Christmas disease.

The Patients

Case 1 (IV, 2, see family tree).—A schoolgirl aged 13 had possibly excessive loss of blood at the onset of menstruation, but the periods thereafter were normal. On two occasions she had bled for 48 hours after dental extractions. Physical examination was negative. In hospital she had further dental extractions, with the insertion of acryclic resin splints, without any haemorrhage.



Family tree of the two cases studied. Case 1 was IV, 2 and Case 2 was IV, 1.

Case 2 (IV, 1).—A typist aged 16, she had not had any incidents to raise a suspicion of abnormal haemorrhage.

The Relatives

III, 4.—This uncle was first investigated after a severe episode of melaena necessitating transfusion of 4½ pints (2.3 litres) of whole blood. There had been five previous incidents of gastro-intestinal bleeding, each of which had necessitated blood transfusion. He had suffered a number of incidents apart from those of gastro-intestinal bleeding, and had been admitted to hospital in childhood after troublesome bleeding from his lower lip. He had required transfusion after dental extraction, and occasional epistaxis was severe. Laboratory investigation established that he was suffering from Christmas disease.

III, 1.—This uncle had died from gastro-intestinal bleeding before we investigated the family. It is probable, though not certain, from the available history that he also had the defect.

III, 3.—This uncle gave no history of abnormal haemorrhage.

III, 2.—The father of the two sisters. He was investigated as part of the family study resulting from the discovery of III, 4. He had also bled after dental extraction for periods exceeding two days. Severe epistaxis had also occurred. Laboratory study showed that he also had Christmas disease.

In none of these brothers was there any history of haemarthrosis. None of the other relatives gave any history of abnormal bleeding.

Methods

The bleeding-time was measured by Ivy's method as described by O'Brien (1951); the tourniquet test was that described by Biggs and Macfarlane (1953); and the platelet count as described by Rees and Ecker (1923), using edetic acid as anticoagulant. The whole-blood coagulation time was measured by the method of Lee and White (1913) as described by Biggs and Macfarlane (1953).

Recalcification times: Mixtures were made of one part of control or test plasma in nine parts of Christmas-disease plasma. Doubling dilutions of this were made in further volumes of Christmas-disease plasma; this plasma was obtained from a patient severely affected with Christmas disease. The recalcification times were assessed by the method described by Biggs and Macfarlane (1957). The one-stage "prothrombin" test was performed as described by Biggs and Macfarlane (1953), using saline brain thromboplastin as prepared by Toohey (1950).

Assessment of the blood thromboplastin system (prothrombin consumption) was carried out (*a*) on whole blood by the method described by Merskey (1950), and (*b*) on recalcified plasma. The use of the prothrombin consumption of recalcified haemophilic or Christmas-disease plasma for the detection and assay of anti-haemophilic globulin and Christmas-factor deficiencies has previously been described (Douglas and Cook, 1957; Douglas and Mair, 1958; Douglas, 1958a).

The thromboplastin generation technique was carried out as described by Biggs and Douglas (1953). In some of the tests chloroform extract of dried brain was used in place of platelets, as described by Bell and Alton (1954). The test was modified to give an assay of Christmas factor in the same way as it can be used to assay anti-haemophilic globulin as described by Douglas (1958b). Normal adsorbed plasma and platelets are kept constant, and the variable consisted of mixtures of normal or test sera in Christmas-disease sera.

Results

The preliminary laboratory investigations of Cases 1 and 2 are set out in Table I.

TABLE I.—*Preliminary Laboratory Investigations in Cases 1 and 2*

Tests	Case 1	Case 2	Normal
Bleeding-time (mins.)	3½	3	2½–7
Platelet count (per c.mm.)	240,000	280,000	150,000–500,000
Tourniquet test	Negative	Negative	Negative
Whole-blood coagulation time (mins.)	9½	9	5–10
One-stage prothrombin time (secs.)	13	13	13
Prothrombin consumption index (average of 2 observations)	27%	17%	Less than 20%
Thromboplastin generation test:			
Patient's adsorbed plasma	Normal	Normal	
,, serum	Abnormal	Abnormal	

Thromboplastin Generation Technique

The significant findings were in the thromboplastin generation technique, where there was a defect in the serum side of the system.

The results in Case 1 are shown in Table II. It will be seen that the difference from the normal serum was not marked, but was a consistent finding on six other separate observations. The essential part of this study was to establish the nature of this serum thromboplastin defect.

TABLE II.—*Serum Defect in Thromboplastin Generation*

Variable Reagents	Incubation Time in Minutes					
	1	2	3	4	5	6
Normal adsorbed plasma + ,, serum	46	20	11	9	10	10
Patient's adsorbed plasma + ,, serum	48	16	14	13	12	14
,, ,, + Normal adsorbed plasma	44	16	14	13	14	13
Patient's adsorbed plasma + Normal serum	25	11	11	11	10	10

Thromboplastin generation technique with M/40 calcium chloride and chloroform brain extract constant.

In Table III the results are shown of the failure of Case 1 serum to correct the serum defect in a known case of Christmas disease as effectively as the normal serum. In this particular experiment the normal reagents were not yielding such a powerful thromboplastin as that in Table I, and the serum defect in Case 1 is even more obvious.

TABLE III.—*Inability of Serum to Correct Christmas-disease Serum in Thromboplastin Generation*

	Incubation Time in Minutes					
	1	2	3	4	5	6
Normal serum	55	31	11	12	11	12
Case 1 ,,	70	76	51	35	13	13
Christmas-disease serum	96	100	76	47	25	23
10% normal serum + 90% Christmas ,,	84	70	35	16	13	13
10% Case 1 serum + 90% Christmas ,,	80	67	56	28	22	20

Thromboplastin generation technique with serum as variable reagent: M/40 calcium chloride, normal adsorbed plasma, and chloroform brain extract are constant.

Comparison of sera from Case 1 and Case 2 in the same experiment demonstrated that the sisters had an identical defect and that the degree of this was the same.

Prothrombin Consumption Technique on Recalcified Christmas-disease Plasma

The results of this are shown in Table IV. It will be seen that the addition of plasma from Case 1 is not nearly so powerful in correcting the defective prothrombin consumption of Christmas-disease plasma as is the normal plasma addition.

TABLE IV.—*Prothrombin Consumption of Recalcified Christmas-disease Plasma. Clotting-times of Fibrinogen in Seconds*

Plasma Addition	Time in Minutes after Addition of M/10 Calcium Chloride					
	10	20	30	40	50	60
Normal	40	46	42	40	39	42
Case 1	16	19	19	18	17	21
Christmas disease	12	12	12	11	12	13

Assays of Christmas Factor and Antihaemophilic Globulin

These assays were performed by the thromboplastin generation method and by the prothrombin consumption technique in recalcified Christmas disease or haemophilic plasma.

In tables V and VI are shown the results, expressed in clotting-times, of the Christmas-factor assays by the thromboplastin generation technique and the prothrombin consumption method on recalcified Christmas-disease plasma.

The results of all the assays on Case 1 and Case 2 and their parents are shown in Table VII. As the father had Christmas disease of only moderate severity the assays were made in comparison with plasma and serum from a severely affected patient with Christmas disease.

TABLE V.—*Assay of Christmas Factor Content of Serum by the Thromboplastin Generation Technique*

Percentage of Normal Serum in Christmas-disease Serum	Clotting-time in Seconds after 6 Minutes' Incubation
50	16
25	17
12	21
6	24
3	32
0	43
Percentage of Case 1 Serum in Christmas Disease serum	
50	23

Thromboplastin generation technique with normal adsorbed plasma and platelets constant, and the serum component of the system variable. The clotting-times represent the mean of five observations.

TABLE VI.—*Assay of Christmas Factor Content of Plasma by the Prothrombin Consumption Method*

Percentage in Terms of Standard Addition		Clotting-times of Fibrinogen in Seconds
Normal plasma	100	61
	50	52
	25	45
	12	32
	6	23
	3	16
	0	14
Case 1 plasma: 100		29

Clotting-times of fibrinogen represent the mean of 11 observations.

TABLE VII.—*Assays of Christmas Factor and Antihaemophilic Globulin in the Two Sisters and Their Parents*

	Christmas Factor	Antihaemophilic Globulin
Case 1 ..	13	74
,, 2 ..	18	82
Father ..	3	79
Mother ..	84	92

The assays are expressed as percentages in comparison with a mixture of 4 normals. In Case 1 the figures expressed are the mean of 11 assays on the prothrombin consumption method and 5 assays on the thromboplastin generation technique. In the others only single assays were made.

Recalcification Times.—The impaired ability of plasma from Case 1 and her father to shorten the recalcification time of plasma from a patient with severe Christmas disease is demonstrated in Table VIII. Their plasmas corrected plasma from a severe haemophiliac as well as did normal plasma.

TABLE VIII.—*Recalcification Times.* (*Clotting-times of Plasma in Seconds*)

	Proportion of Addition to Christmas-disease Plasma					
	1/10	1/20	1/40	1/80	1/60	0
Control	114	156	201	270	319	545
Case 1	316	320	361	401	433	
Father	363	392	408	476	492	

Discussion

The object of this paper is to report the cases of two sisters, heterozygous for the defect of Christmas disease. As daughters of a man with this condition they are necessarily transmitters of the condition. These two sisters have a demonstrable deficiency of Christmas factor; this abnormality can be shown on recalcification time, and thromboplastin generation and prothrombin consumption techniques. On clinical grounds it was impossible to tell with certainty that these two sisters had an abnormality. The older sister gave no history of abnormal tendency to bleed and the younger sister gave only a borderline history of abnormality.

The inheritance of the Christmas-factor deficiency in the two sisters is likely to be due to the incomplete recessivity of the gene, as there was no evidence to suggest that either patient was homozygous for the abnormality.

Abnormal prothrombin consumption and/or abnormal thromboplastin generation in transmitter females has also been reported by Rosenthal and Sanders (1954), Ramot *et al.* (1955), Reed (1955), Hule and Nešpůrková (1956), and Firkin (1958). Hardisty (1957) has also reported Christmas-factor deficiency as low as 8% in a woman whose sister had a Christmas factor level of 65%. He considered that the wide difference in the two Christmas-factor levels was evidence of a variable expressivity in the gene apart from its incomplete recessivity.

Summary

A deficiency of Christmas factor in two sisters has been shown by several techniques (recalcification times, thromboplastin generation, and prothrombin consumption).

The father of the two sisters suffers from Christmas disease of relatively mild severity.

We are grateful to Professor L. J. Davis and Dr. A. Dick for guidance in the preparation of the manuscript, and to Mrs. Kathleen Hume for valuable technical assistance. One of us (A. S. D.) is grateful to the Advisory Committee on Medical Research for Scotland for a grant for equipment and to the Medical Research Council for a grant for technical assistance. The family study was included in a thesis submitted for the degree of M.D. to Aberdeen University by I. A. C.

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Medical Memoranda

Jaundice during Treatment of Myelomatosis with M & B 938

The use of M & B 938 (4-4'-diamidinodiphenylamine dihydrochloride) for the first time in myelomatosis has been reported (Ward, 1958a, 1958b). Of the first ten patients treated one had complete relief of bone pain, a fall in the E.S.R., and recalcification of osteolytic lesions. He is still well five years after treatment. In a second patient previous treatment with urethane had been without effect, but during treatment with M & B 938 a palpable rib-tumour disappeared and pain was relieved. A third patient had severe pain in the back despite previous radiotherapy to the area. The pain vanished during treatment with M & B 938. In the other patients there was no obvious benefit.

It is worth noting that jaundice has occurred in two out of these 10 patients who have received M & B 938 for myelomatosis.

CASE 1

A man aged 36 had myeloma deposits in the skull and sacrum. He was given six intravenous injections of M & B 938 daily at Charing Cross Hospital, starting on August 17, 1953. The doses varied from 0.1 g. to 0.25 g. A further dose of 0.1 g. was given at home on August 29. The total dosage was 1.27 g. The last injection was followed by a rigor, and the patient developed pyrexia and an urticarial rash on the neck. On September 3 he had jaundice associated with pale stools and dark urine. The liver was enlarged, but the spleen was not palpable. On September 8 the thymol turbidity was over 10 units, but the alkaline phosphatase was only 4 King-Armstrong units. On September 25 the jaundice was fading, but the alkaline phosphatase had risen to 20 K-A units.

By mid-October the jaundice had cleared, and on December 9 the thymol turbidity was 2 units and the alkaline phosphatase 6 units.

Another course of M & B 938 was begun in January, 1955. On this occasion a total dosage of 1.7 g. was spread over five weeks. There was no jaundice.

CASE 2

A man aged 59, with severe anaemia due to myelomatosis, had been treated for 2½ years with vitamin B_{12}, urethane, and blood transfusions. Treatment with M & B 938 was begun on May 14, 1958, at Charing Cross Hospital. The dosage was 0.1 g. twice weekly to a total of 0.9 g. During the course two blood transfusions were given without a reaction. On June 8 the patient had vomiting and shivering, and three days later developed jaundice associated with pale stools and dark urine. The liver was enlarged but the spleen was not palpable. On June 15 the serum bilirubin was 5.3 mg./100 ml., the alkaline phosphatase was 6 K-A units, and the prothrombin time was prolonged. Bile salts and bilirubin were present in the urine but urobilinogen was absent. On June 27 the thymol turbidity was 1 unit. Prednisolone, 10 mg. thrice daily, was given for a week. On July 18 the jaundice had faded and the serum bilirubin was 1.9 mg./100 ml. Liver biopsy showed marked distension of the bile canaliculi by bile. This change was mainly localized to the centrilobular zones. The parenchyma and portal tracts appeared healthy.

COMMENT

It seems to be very probable that the jaundice in both these cases was due to the action of M & B 938 upon the liver. The elevation of alkaline phosphatase in Case 1 and the histological picture of bile stasis without parenchymal damage together with a negative thymol turbidity test in Case 2 are suggestive of jaundice due to cholangiolitic obstruction rather than of jaundice due to parenchymal liver damage. Although it is unjustifiable to generalize from only two cases, the analogy between the occurrence of jaundice in these two patients and jaundice due to chlorpromazine is obvious. A further point of similarity is that jaundice in Case 1 was preceded by marked systemic upset, including the appearance of an urticarial rash: an allergic basis for chlorpromazine jaundice, as well as for jaundice following the administration of thiouracil, methyltestosterone, and sulphadiazine, has been suggested (Werther and Korelitz, 1957).

It has been shown by Henry and Grindley (1942) and Hampton (1947) that the chemically related drug stilbamidine is highly cumulative. Although no definite information is available at the moment, this may well be true of M & B 938. Moreover, experience suggests that nothing is lost therapeutically by spreading treatment over many weeks.

We consider it is wise not to exceed a dose rate of 0.1 g. twice weekly or a total of 2 g. in any one course of treatment. Our current practice is to give 0.1 g. twice weekly for two weeks and thereafter once weekly.

We thank Dr. R. Moore Patterson and Dr. E. C. Warner for permission to publish the case histories, and May & Baker Ltd. for supplies of M & B 938.

A. M. DENMAN, M.B., B.S.,
Formerly House Physician,
Charing Cross Hospital, London.

H. W. C. WARD, M.B., M.R.C.S., D.M.R.T.,
Radiotherapy Registrar,
St. Bartholomew's Hospital, London.

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Adrenal Apoplexy — A Case Report

The following case of adrenal apoplexy, while strikingly similar to many cases previously recorded, is placed on record with a reminder that more frequent consideration might be given to the diagnosis.

CASE REPORT

On August 10, 1957, a heavily built miner aged 62 was admitted to hospital. He was pale, unconscious, sweating profusely, pulseless, and had an irregular sighing respiration. His wife said he had vomited clear frothy material and then collapsed with severe pain in the left submammary region and in the left hypochondrium. During the previous four months he had often complained of similar but less severe pain, and had been off work for four days with dizziness and weakness. A perforated duodenal ulcer had been repaired a year previously, otherwise he had always been well.

Several doctors examined him, and except that one suspected a mass in the left hypochondrium they found no other physical signs. A very tentative diagnosis of coronary occlusion was made, and resuscitation with intravenous infusion of 5% dextrose solution containing noradrenaline was begun. The blood-pressure, previously unrecordable, rose rapidly, but it was difficult to maintain a stable level, as minute alterations in the rate of flow caused wildly disproportionate excursions of pressure. After eight hours he was again conscious but extremely restless. He vomited clear froth in small quantities and complained of severe upper abdominal pain. There was moderate abdominal distension but no rigidity, and a tender fixed mass about the size of a closed fist was easily recognized. There were no signs of free fluid or gas in the abdomen. No bowel sounds were heard. Radiographs of the abdomen and electrocardiograms were normal.

Such possibilities as rupture of the renal or splenic arteries and perforation of a tumour of the stomach or colon were considered. The extreme collapse suggested the possibility of suprarenal haemorrhage, but the presence of the mass in the left hypochondrium was thought not to favour that diagnosis. This was mistaken, and the apparent rapid increase in size of the mass was a feature whose special significance was not appreciated.

An exploratory laparotomy was done under general anaesthesia, using a right paramedian incision with a horizontal extension to the left. A large, tense, non-pulsating cystic retroperitoneal tumour was felt in the left upper abdomen. The descending colon was mobilized medially and the tumour was readily lifted out with little bleeding. There was no recognizable pedicle, though a few dense adhesions to the posterior abdominal wall had to be clamped and ligated. Golden-yellow suprarenal tissue was present in the upper pole, and elsewhere the tumour was fleshy and disrupted by bleeding. It contained about 20 oz. (570 ml.) of fluid dark-red blood in a central cavity with irregular walls varying from ¼–½ in. (0.6–1.3 cm.) thick. The colon was allowed to fall back into place and the abdomen was closed. Hydrocortisone was added to the infusion and the patient improved, but only gradually. In 12 hours the systolic blood-pressure was stable in the region of 100 mm. Hg and intravenous fluids were discontinued. The patient's progress thereafter was untroubled, and he went home well on the fourteenth day and has remained so. On histological examination the tumour proved to be an adenoma of the adrenal cortex.

COMMENT

Rayer (1837, 1839) illustrated an identical case. Mattei (1863, 1883) also recorded similar cases, and Arnaud (1900) wrote an exhaustive review of the literature and added his own experiences.

Many cases are apparently quite fortuitous and the haemorrhage may be of all degrees from little more than hyperaemia to disruption of the gland with profuse intraperitoneal bleeding. It occurs at any age on either side or both sides.

Generalized infections complicated by suprarenal haemorrhage have been recorded by Parrot (1872), Langlois and Charrin (1893), Roux and Yersin (1896), Still (1898), Waterhouse (1911), Friderichsen (1918), and Fox (1942).

Cysts and tumours were associated abnormalities in the cases described by Thorstad (1942), Griffiths (1950), Gilliland and Daniel (1951), Jelliffe (1952), Ellis, Dawe, and Clagett (1952), Mackenzie (1955), and Grogono (1956).

Many of the authors quoted here have considered thrombosis of the adrenal veins to be a possible cause, but this is difficult to establish (Maclean and Ironside, 1958). Trauma during birth or from too vigorous resuscitation of the asphyxiated newborn infant has been blamed. Asphyxia itself and its associated hypertension may be responsible (Corcoran and Strauss, 1924).

The experiences of Keele and Keele (1942) and Dewhurst (1951) call for the most careful consideration of this condition in the diagnosis of abdominal catastrophes in pregnancy, especially when that is complicated by toxaemia or hypertension. Their cases were subjected to laparotomy and this was negative, or a little blood-stained fluid was found in the upper abdomen. These authors stress the need in such circumstances to examine the suprarenal regions with this possibility in mind.

The literature records a sad succession of fatalities. The cause of death in unilateral cases is obscure. Lavenson (1908) suggested that the sudden destruction by haemorrhage of a hormone-producing tumour of the cortex may cut off the accustomed high level of circulating hormones, the other gland being atrophic.

In a few instances recovery has followed a variety of surgical procedures of varying magnitude (Corcoran and Strauss, 1924; Edelman, 1945; Oddo, 1946; Ellis *et al.*, 1952), and as early as 1928 Goldzieher and Greenwald succeeded with conservative treatment, using their own preparation of cortical extract.

We acknowledge with thanks permission from Dr. E. S. Frazer and Mr. Weldon Watts to publish this record.

ALISTAIR B. M. CURRIE, F.R.C.S.,
SHROFF T. NAYAK, M.B., Ch.B.,
Shotley Bridge Hospital.

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Reviews

BLOOD GROUPING

Practical Blood Grouping. By F. Stratton, M.D., D.Sc., D.P.H., and P. H. Renton, M.D., B.Sc. (Pp. 331+xxiv; illustrated. 42s.) Oxford: Blackwell Scientific Publications. 1958.

During the lifetime of Landsteiner the intellectual urge behind blood-grouping research came mainly from the field of immunology. Since then, largely under the influence of Fisher and Race, genetics has supplied the main impulse, and serology has served, in the main, as a tool—one of superb effectiveness—for the dissection and display of the human germ-plasm. Nevertheless it must not be forgotten that the main clinical manifestations of the blood groups—transfusion reactions and haemolytic disease of the newborn—are mediated through serological mechanisms, and there has long been an unfilled need for a scholarly and critical work on the immunological aspects of blood grouping. This lacuna has at last been filled by the present book.

The authors have themselves been responsible for important advances in blood-grouping practice and theory, and combine a thorough knowledge of the literature with an unrivalled experience of applying serological principles to practical transfusion work. The book is therefore one which should be read by every pathologist in charge of any aspect of blood transfusion, as well as by senior technicians. More junior technicians will, however, find it somewhat heavy going, and it cannot therefore be put into their hands as a day-to-day laboratory guide.

The list of contents shows that the book deals very fully with every aspect of blood grouping, from the theory of antigen-antibody reactions to the organization of large-scale grouping and antenatal testing. The chapter on the cross-matching test is one of the best accounts, and almost certainly the most complete, yet written on the subject. The illustrations are very good, and nowhere else is there to be found such a clear, complete, and critically interpreted set of photomicrographs of haemagglutination. There is a full index. It is unfortunate, however, that the excellence and completeness of the material are not paralleled by good arrangement and ease of reading. The style is discursive, and, with some notable exceptions, major subjects are broached without an introduction giving definitions and a clear statement of the theoretical background.

The methods recommended are all of proved reliability, and most of the criticisms that can be made of them refer to minor points of technique such as are bound to differ from one laboratory to another. Some rather more important points of disagreement must, however, be mentioned. The most effective source of human complement for titrating anti-A and anti-B haemolysins (p. 56) consists neither in AB serum nor in absorbed O serum, which are recommended by the authors, but in a serum of the same group as that under test, always obtained in any one laboratory from the same donor and selected as containing adequate complement without haemolysins. With such a source, a lytic test, contrary to the authors' view (p. 133), becomes one of the most useful means for indicating whether an anti-A or anti-B serum is of immune origin. The only tube tests recommended for the detection of the D antigen (pp. 184–5) involve the use of saline-agglutinating anti-D serum. This is particularly unfortunate in a book which will rightly be used as a guide in the planning of transfusion centres in newly developed countries, for in such countries (and, indeed, even in Great Britain) D testing would be greatly restricted or even impossible if most of the tests were not done with the relatively much more abundant albumin-agglutinating anti-D, albumin or papain being used as an adjuvant. The recommendation (p. 236), in the transfusion of newborn infants, to use blood of homologous group, even if incompatible with the mother's ABO group, will not be accepted by any means universally.

It is inevitable in such a work as this that some of the inclusions or omissions should be open to criticism, but it can nevertheless be said without hesitation that the book is the best available of its kind, and it should be in every laboratory concerned with blood grouping. It is to be hoped, however, that in a second edition the authors will partly rewrite and very considerably rearrange their excellent material so as to make it more easily readable.

A. E. MOURANT.

SCANDINAVIAN OTORHINOLARYNGOLOGY

Nordisk Lærebog i Oto-Rhino-Laryngologi. Edited by C. O. Nylén, H. C. Andersen, Truls Leegaard, and Urpo Siirala. (Pp. 482; illustrated. Dan.kr. 78.) Copenhagen: Ejnar Munksgaard. 1958.

Medical students in the Scandinavian countries and Finland have until recently suffered a certain handicap in having to study their subjects in a foreign language, usually English or German. So far as otorhinolaryngology is concerned they have now been provided with a textbook in their own language or one easily understood by them. The book is the outcome of collaboration between ear, nose, and throat surgeons from the four countries under a distinguished editorial committee of four, one from each country, headed by Professor Nylén, of Uppsala. Each author writes in his own language, those from Finland writing in Swedish.

The subject is very fully covered, and there are chapters on radiology and radiotherapy as applied to diseases of the ear, nose, and throat, as well as articles on plastic surgery, speech defects, and diseases of the salivary glands and lacrimal sac. In view of this wide scope it might be suggested that a short chapter on local and general anaesthesia as applied to ear, nose, and throat surgery could with advantage be included in a later edition.

As might be expected in a symposium, there are occasional variations in approach and in the general level of information provided. As a whole, however, it is homogeneous with little overlap, and fulfils its purpose as a textbook for medical students and a reference book for general practitioners. In fact, it probably provides more advanced teaching than would be required for simple qualification in Great Britain and could be used by students for higher examinations with certain implementations, particularly as regards operative surgery, which is here dealt with mainly in principle with little technical detail. In their attitude to the subject and in their teaching the writers approximate closely to current British teaching and practice.

The book is attractively produced with good print and some excellent colour plates. The index might possibly be a little more detailed. This is a textbook of high quality and a praiseworthy result of international collaboration. It deserves every success and will undoubtedly attain it.

J. W. S. LINDAHL.

ALLERGY

Allergie. By 24 Contributors. Edited by K. Hansen. Third edition. (Pp. 1,212+xxvi; illustrated. DM. 187.) Stuttgart: Georg Thieme Verlag. 1957.

Von Pirquet's enigmatic term "allergy"—an "altered reactivity," difficult to define, impossible exactly to determine—embraces, besides the known allergic diseases such as serum sickness and hay-fever, the probable ones like asthma and collagen diseases, and a formidable array of syndromes suspected (sometimes on insufficient evidence) of having an allergic basis. To distinguish these various types requires careful clinical analysis and critical evaluation. This is the guiding principle of the important textbook which has been edited by the distinguished allergist Professor Hansen with the collaboration of 23 eminent scientists and clinicians. Rössle gives a historical introduction and a review of the pathological anatomy of allergic diseases. Klinge describes the experimental pathology, based on his classical work on the characteristic lesions produced in the joints, heart, and blood-vessels of rabbits by topical injection of horse serum. Hans Schmidt discusses serology, reagin testing, side-effects of allergic tests, and serum sickness. Hansen gives an excellent and detailed account of the pathological physiology of the allergic state, diagnosis, allergenic agents, hay-fever, asthma, and the role of allergy in digestive and nervous diseases.

Other specialists deal with allergy in the skin, mouth, eyes, ear, nose and throat, cardiovascular and haemato-poietic systems, liver, and kidneys; the rheumatic group; infectious and parasitic diseases; and the paediatric problems of allergy. Further chapters are devoted to pharmacology and treatment, heredity, drug allergy, industrial diseases, and allergic manifestations in animals. In order to save space few references to the literature are given, the reader being referred to the relevant *Zentralblatt*; this defect, however, will be remedied in future editions.

The book is beautifully written in easy German, well produced, and provided with many good illustrations. It contains an enormous amount of information, and should be very helpful to everyone interested in this fascinating subject.

C. P. GILES.

EXPEDITION TO GREENLAND

Venture to the Arctic. Edited by R. A. Hamilton. (Pp. 283 +xiv; illustrated. 5s.) Harmondsworth, Middlesex: Penguin Books. 1958.

I read this book twice; this must be rare for a reviewer. In 1938 I said at the Royal Geographical Society, "The fact remains that we go to Everest not for these reasons [of national prestige] at all, but . . . simply because it is fun. . . . I do not think we are any longer justified in spending large sums of public money in satisfying these private urges. . . . I do not think even private expeditions are justified in losing the outstanding opportunities which they have for making valuable scientific researches." In 1938 this was trailing my cloak indeed, but to-day such views are normal and commonplace. The expedition here described shows well how the pursuit of scientific objects can justify the fun as well as the money expended.

To readers of this journal Masterton's chapter on "Medical Aspects" will be the most interesting one, but I hope that even doctors will read on and, after finishing Peacock's admirable chapter, feel themselves better geologists than they ever hoped to be. Masterton is readable and constructively critical on diet and sanitation, and lays proper stress on the need to consider individual taste. Lewis on "Physiology" is almost as readable and even more instructive.

Perhaps my keenest memory of this admirable little book is of the difficulties which this small band of scientists faced. They stopped carrying soap, preferring rock specimens; they got frost-bite from falling into frozen lakes; they were delayed in their work by a ferocious bull musk-ox who resented their presence and had no interest in glaciology; and only those who have already tried to use scientific apparatus at temperatures well below zero will fail to learn something of the difficulties inherent in an enterprise such as this. I have eaten pemmican, the most awful food I know. These men lived for nine weeks on nothing else, and all the same had fun and brought back information of great worth.

For five shillings you can have an evening of escapism and help them to go back to Greenland.

RAYMOND GREENE.

EPIDEMIOLOGY IN EGYPT

Epidemiology of Communicable Diseases. By Ahmed Mohamed Kamal, D.P.H.(Camb.). (Pp. 567+iii.) Cairo: Anglo-Egyptian Bookshop. 1958.

This book is concerned with the epidemiology of the communicable diseases of Egypt, but has in fact a much wider application, and is a useful guide to epidemiology throughout the subtropics and tropics, though of course certain diseases which are not found in Egypt are not discussed.

The opening chapters deal with the general principles of epidemiology. The infectious process, immunity, control of infectious disease, and disinfection and disinfestation are discussed in adequate detail and with commendable lucidity, though a footnote on page 78 is perplexing.

The second part of the book comprises some 26 chapters on the different infectious diseases which are prevalent in Egypt. Most of these are by the principal author, but there are sections by six invited contributors who have special experience of the subjects on which they write. The chapter on helminthic diseases is disappointing, owing, as is explained in the preface, to some misunderstanding, while bilharziasis, which is one of the most important, if not the most important, causes of ill-health in Egypt is dealt with in a brief seven pages. No doubt this will be put right in future editions. Many of the sections, and in particular those from the pen of the principal author, are full and authoritative, and indicate wide experience and sound and critical judgment. The chapters dealing with enteric and dysentery group infections, the rickettsias, cholera, plague, and spirochaetal diseases are of particular interest to those who have little first-hand acquaintance with these infections, and show clearly the difficulties

with which the tropical epidemiologist is faced. It is interesting to note that the author has only a limited faith in the value of antityphoid inoculation, largely because of its apparent failure to protect British troops in Egypt in the post-war years. It is gratifying to note that he completely refutes the oft-repeated suggestion that these same troops were responsible for initiating the cholera outbreak in 1947.

As is inevitable in a book written in a language foreign to the author, there are some spelling and grammatical errors, none of which is of any significance; nevertheless it would be well to have future editions proof-read by someone whose native language is English. Both as a textbook for the student and as a reference book for the practitioner in the tropics this volume can be confidently recommended.

J. S. K. BOYD.

HISTORY OF MEDICAL EDUCATION AND CARE IN CHICAGO

Medicine in Chicago, 1850–1950. A Chapter in the Social and Scientific Development of a City. By Thomas Neville Bonner. (Pp. 302+xvii; illustrated. 42s.) London: Holborn Publishing Company Ltd. 1958.

This book was commissioned by the Chicago Medical Society, though they do not agree with all its contents. It is medical history with a difference. The author is a layman, trained in historical research, and the emphasis is on the meaning and significance of medical progress rather than on how medical discoveries were made. It tells the thrilling story of how Chicago grew in just over 100 years from a small disease-ridden settlement on low land at the mouth of a river to the great metropolis and medical centre it is to-day. Foreign visitors who confine their knowledge of Chicago to the splendours of Michigan Avenue and the pleasant suburbs on the lakeside regard it as a very fine city, but those who penetrate to the stockyards and packing houses and the densely populated slums realize that, like all large cities, it is good only in parts. It has had many vicissitudes, the worst misfortune being the great fire of 1871, which destroyed the famous Rush Medical College and six hospitals as well as the homes of 93,000 people.

Chicago has produced, or attracted, many distinguished doctors, and the text is interspersed with vignettes of most of them. Reference is made to their disagreements and quarrels, from which no medical community seems to be free, and how, in most cases, they overcame opposition. They include Dr. Nathan Smith Davis, sen., the founder of the Americal Medical Association, his son Nathan Smith Davis, jun., and now Nathan Smith Davis III. The evolution of the several medical colleges is well described. Adverse comments made by the then editor of this journal, when on a visit there in 1893, on the water-supply and the paucity of the vital statistics are quoted. In Chicago one expects the unusual, but it must be very rare for a professor of obstetrics to close his career by shooting indiscriminately at his students, as happened at the turn of the century.

There are 40 pages of notes at the end of the book, and it would have been more convenient for the reader if they had appeared as footnotes on the pages concerned. The bibliography and the index are excellent. It is an interesting book, easily read, and can be recommended warmly.

ALLEN DALEY.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Food Poisoning. Food-borne Infection and Intoxication: Nature, History, and Causation. Measures for Prevention and Control. By Elliot B. Dewberry, M.B.E. Fourth edition. (Pp. 411+xvi; illustrated. 45s.) London: Leonard Hill (Books) Ltd. 1959.

A Final Study in the Nature of Disease. By J. E. R. McDonagh, F.R.C.S. (Pp. 376+xx. 30s.) London: William Heinemann Medical Books, Ltd. 1959.

A Guide to Antibiotic Therapy. By Henry Welch, Ph.D. (Pp. 69.) New York: Medical Encyclopedia, Inc. 1959.

The Anti-Globulin (Coombs) Test in Laboratory Practice. By I. Dunsford, Ph.D., M.I.Biol., and Jean Grant, F.R.C.P. (Pp. 120+xiii 12s. 6d.) Edinburgh and London: Oliver and Boyd. 1959.

Institutional Neurosis. By Russell Barton, M.B., M.R.C.P., D.P.M. (Pp. 57; illustrated. 8s. 6d.) Bristol: John Wright and Sons, Ltd. 1959.

The Antecedents of Man. An Introduction to the Evolution of the Primates. By W. E. Le Gros Clark, F.R.S. (Pp. 374 +vii; illustrated. 21s.) Edinburgh: The University Press. 1959.

The Battle for the Soul. Aspects of Religious Conversion. By the Reverend Owen Brandon, M.A., A.L.C.D. (Pp. 96. 4s. 6d.) London: Hodder and Stoughton. 1960.

A Catalogue of the Portraits and Other Paintings, Drawings, and Sculpture in the Royal College of Surgeons of England. By William LeFanu. (Pp. 119+xii; illustrated. 30s.) Edinburgh and London: E. and S. Livingstone Ltd. 1960.

The Prescriber's List of Proprietary Medical Products. Issued by the Unichem Association of Privately Owned Pharmacies. (Pp. 381. 15s.) London: Unichem, Ltd. 1960.

Every-day Prescriptions with Hints on Treatment (with more than 300 Prescriptions). By Prankumar Guha, M.B., Major, I.M.S.(Retd.). (Pp. 319+vii. Rs. 6.) Calcutta: S. Bhattacharya and Co. 1959.

L'Agopuntura Cutanea nella Cura del Dolore. By Piero Orlandini. (Pp. 135+xiv; illustrated. L. 1,000.) Rome. 1958.

Research on Novocain Therapy in Old Age. In English Translation. A collection of seven papers from *Die Therapiewoche*, 1956–1957, by Professor Anna Aslan, M.D., and co-workers at the C.I. Parhon Institute of Geriatrics, Bucharest, Rumania, and Professor C. M. Bürger, M.D., Professor F. H. Shulz, M.D., and U. Köhler, M.D., and E. Mampel, M.D. (£5.) Consultants Bureau, Inc. London: Chapman and Hall. 1959.

Biophysical Science. A Study Program. Planned and edited by J. L. Oncley, Editor-in-Chief, with F. O. Schmitt, R. C. Williams, M. D. Roxenberg, and R. H. Bolt. Published in the *Reviews of Modern Physics*, January and April, 1959. (Pp. 568 +viii; illustrated. 52s.) New York: John Wiley and Sons, Inc. London: Chapman and Hall. 1959.

Antibiotic Therapy for Staphylococcal Diseases. Edited by Henry Welch, Ph.D., and Maxwell Finland, M.D. (Pp. 208+ xii. $4.50.) New York: Medical Encyclopedia, Inc. 1959.

Simposio sulla Tripsina e Chimotripsina. Atti della Societa Lombarda di Scienze Medico-Biologiche, Milan, April 18–19, 1959. Edited by W. Montorsi, P. Pietri, and A. Peracchia. (Pp. 235; illustrated. L. 3,000.) Milan: Minerva Medica. 1959.

Immunological and Haematological Surveys. Report of a Study Group. (Pp. 35. 1s. 9d.) Geneva: World Health Organization. London: H.M. Stationery Office. 1959.

Radiation Biology. Proceedings of the Second Australasian Conference on Radiation Biology held at the University, Melbourne, December 15–18, 1958, by the Australian Radiation Society. Edited by J. H. Martin. (Pp. 304+xi; illustrated. 63s.) London: Butterworths Scientific Publications. New York: Academic Press, Inc. 1959.

Chemical and Molecular Basis of Nerve Activity. By David Nachmansohn. (Pp. 235+xi; illustrated. $7.50.) New York and London: Academic Press. 1959.

Africa—Social Change and Mental Health. Report of a Panel Discussion held at the United Nations, New York, March 23, 1959, by the World Federation for Mental Health. (Pp. 40. 3s. 6d.) London: H. K. Lewis and Co., Ltd., for the World Federation for Mental Health. 1959.

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RETROSPECT TO PAY CLAIM

The Report of the Royal Commission on the Remuneration of Doctors and Dentists in the N.H.S. will be published on February 18. The Commission was set up almost exactly three years ago. Under the energetic and skilful leadership of Dr. S. Wand, Chairman of Council, the B.M.A. has submitted cogent memoranda of evidence, and its representatives have appeared on several occasions before the Commission itself. The reports of the Commission's cross-examination of various professional bodies and individuals were published at length in the *Supplement* at the time. And in this week's *Supplement* we give an account of the running dispute over pay with successive Ministers of Health since 1948. The Reports of the two Spens Committees were published in 1946 and 1948. They were crucial to the decision of the medical profession to enter the National Health Service. They gave a guarantee of a standard of living to a liberal profession about to sacrifice much of its traditional freedom in order to provide a comprehensive medical service to the people of Britain under the auspices and, indeed, control of the State.

The next important date was 1952, when Mr. Justice Danckwerts's award to general practitioners of a betterment factor of 85% for the years 1948–9 and 1949–50 and of 100% for the year 1950–1 was the first realistic assessment of what the G.P. Spens Report meant. Dr. S. Wand's energy and persistence in advocacy achieved this important result for general practitioners in the Health Service. The result was a shock to the Government, and ever since then it has persistently avoided the logical consequence of Mr. Danckwerts's adjudication. We may expect to see in the recommendations of the Royal Commission a last move to bury the two Spens Reports. So long as the Government, in deciding what action to take on the Royal Commission's advice, gives an alternative charter of terms of service which will satisfy the profession, then, and then only, will the profession, we believe, be content to put the Spens Reports in its historical archives.

The terms of reference of both the Spens Committees and of the Royal Commission properly include a comparison of doctors' earnings with those of other professions. But no other profession—the Law, for instance—has consented to become "nationalized." The medical man working in the National Health Service in these years of inflation has not been able to make the adjustments others have made in all walks of life to maintain a standard of living. As things stand, the veterinary profession, for example, begins to offer an attractive alternative livelihood for the youth of to-day. That this is not a fanciful suggestion is borne out by an interesting article in the authoritative weekly *The Economist*, which states: "... the vet's position is one that many in the profession [veterinary] now compare favourably with that of the medical G.P., which they see as going down in the promiscuous drudgery of the health service."

The problems facing both profession and Government are serious and urgent. It is not just a question, or primarily a question, of getting a betterment factor of such and such a percentage. The profession has, of course, been badly treated. It has suffered endless frustrations, and has borne them with remarkable patience. It has been underpaid. But it would above all welcome the beginning of a new era in which it could co-operate in a fruitful partnership with the State in evolving a National Health Service in which doctors would be content to work at their job of looking after the ill and the injured. If this cannot be secured, if the partnership with the State continues to be an uneasy relationship accentuated at intervals with crises over pay and conditions of work, then Medicine will cease to be a calling to which the idealism and ambitions of able youth will respond.

The Report of the Royal Commission will have to be studied with care and time for reflection. The profession will at least owe this in recognition of the hard labour of the able group of men and woman who, under the patient chairmanship of Sir Harry Pilkington, have exhaustively looked into the problems of doctors in the variegated structure of the N.H.S. If we seize first upon points on which there may be agreement, it will be easier to resolve points of disagreement. But whatever the nature of the Report and its recommendations, it will be the Government that will decide what can be done or not done. It will be with the Ministry that the hard task of negotiation will be undertaken, and behind the Ministry there will be the Treasury. Whatever the financial benefits that may come to the profession out of all this, they will be of secondary importance to the continued evolution of Medicine in a way that will attract the capable and the clever youth of to-day and to-morrow.

[1] *The Economist*, February 6, 1960, p. 504.

SHOES AND FEET

The relationship of footwear to deformities and other troubles of the feet is a subject of perennial interest. Especially is this true of children's feet. Questions in Parliament on it were reported recently in this journal (February 6, p. 435), and the Parliamentary Secretary to the Ministry of Health announced that a privately financed independent survey of children's feet at various ages was to be undertaken "as a research project."

Some maintain that but for the effects of unsuitable footwear (and apart from congenital disease and gross injury) there would be no foot troubles. By implication such an attitude suggests that structural and functional perfection is inherent in the human foot. On the other hand, there is a school of thought which, while not denying that a foot may be deformed by external means—as an extreme example the bound feet of Chinese ladies of a previous generation may be instanced—nevertheless believes that many of the common foot deformities may be at least partly determined by inherent weaknesses in the foot itself combined with the restricted stereotyping of foot movements which civilized life imposes. This idea was first propounded many years ago by N. C. Lake.[1]

One of the main difficulties of the first viewpoint is to explain the deformities which are found among people whose footwear cannot be criticized and even among people, though less commonly, who habitually go unshod. There are now few places left in the world where a totally unshod population can be observed, and there are also racial differences of structure and function to be considered which make comparison difficult. Nevertheless evidence exists to show that some of the common foot deformities of civilized communities do also occur in those where shoes are not worn. N. A. Barnicot and R. H. Hardy,[2] for instance, studied West Africans and concluded that: "Occasional valgus deviation of more than +20° is sometimes found in barefooted Africans. . . . Deviations of more than +10° are not infrequent in Africans below 25 years of age. . . . It is clear that, whatever may be the cause of such deviations in Africans, footwear can play no part in their production." Again, letters from recent issues of the journal may be quoted: "Foot-disabilities are not caused by ill-fitting shoes, as I have seen many of these disabilities in the feet of Negroes and Chinese who have never worn footwear of any kind."[3] "Most deformities of the feet and toes are developmental, and it will be necessary to alter the genes rather than the child's footwear in order to prevent them."[4] It is impossible therefore to accept the contention that all foot disabilities are attributable to ill-designed footwear, though it would be equally absurd to assert that such footwear had no effect on the feet. And so interest centres on what characteristics of footwear can be considered bad, and also on the age at which any such effects are likely to be most harmful.

While there is usually disagreement on the first question, all will concur that most harm arises during growth. It is for this reason that several surveys of schoolchildren's feet have been carried out. An early one was that by M. Emslie in London,[5] which paid particular attention to the shoe-purchasing habits of parents. In 1941 E. H. Wilkins[6–10] published the results of an extensive survey of over 3,000 children in the Birmingham district, and recently the health authorities of Stirlingshire[11] have carried out another. There have been several others, and in addition the British Boot, Shoe, and Allied Trades Research Association has investigated the problem by surveys and researches on the form of shoes.

The statistical results of these surveys are roughly in agreement, but it can nevertheless be questioned whether the criteria of abnormality were always uniform or justified. Some of them—for example, the degree of pronation or the angle of deviation of the great toe, which should be considered a valgus deformity—must surely be difficult of assessment. However that may be, most observers agree that an excessive number of girls (aged 5–15 years) as compared with boys have hallux valgus. Thus in Stirlingshire the incidence rose from 2.3% at 5 years to 14.8% at 15 for boys, while for girls the corresponding figures were 1.6% to 54.6%. This disproportionate increase starts before the age of 9, up to which time there is practically no difference in the footwear of the two sexes, yet there seems to be no other way of accounting for it than by the effect of footwear. Lake[12] maintains the most important factor is the wearing of higher heels.

In the Stirlingshire survey the reasons why footwear was considered unsatisfactory are tabulated, and the two most frequent causes were the wearing of "casual" shoes and footwear being too small. "Casual" shoes are not defined, but if the term is

[1] Lake, N. C., *Brit. med. J.*, 1942, **1**, 31.
[2] Barnicot, N. A., and Hardy, R. H., *J. Anat.* (*Lond.*), 1955, **89**, 355.
[3] Simpson, W., *Brit. med. J.*, 1959, **1**, 1530.
[4] Hyman, G., ibid., 1959, **1**, 1189.
[5] Emslie, M., *Lancet*, 1939, **2**, 1260.
[6] Wilkins, E. H., *Med. Offr*, 1941, **66**, 5.
[7] —— ibid., 1941, **66**, 13.
[8] —— ibid., 1941, **66**, 21.
[9] —— ibid., 1941, **66**, 29.
[10] —— ibid., 1941, **66**, 37.
[11] Freebairn, C., Scott, G. A., and Neil, R. E., ibid., 1959, **102**, 55.
[12] Lake, N. C., *Ann. roy. Coll. Surg. Engl.*, 1956, **19**, 23.
[13] Public Information Leaflet No. 7, 1950.

applied to low-heeled shoes with soft uppers it is difficult to harmonize this with the recommendation of the trade research association[13] that "sandals, light indoor shoes, slippers, or plimsolls, are good for a change under certain conditions." But the literature on footwear is full of anomalies: surely a warning not to be too dogmatic. Indeed, the Stirlingshire survey emphasizes this point, for it shows that, of the children with unsatisfactory footwear at the age of 16, 94 had some foot defect while 115 were judged to be without defect. As the authors themselves say, "There is therefore no simple correlation between foot defects and unsatisfactory footwear." On the other hand, everyone can agree that footwear of proper size to allow for extension of toes and for growth is of prime importance. A point of interest brought out by this survey, to which attention was drawn in the earlier survey of Emslie, is the high percentage of young children who have shoes bought for them without fitting or even being in the shop at purchase. The figures indicate that there is twice as much chance of having a badly fitting shoe if the size is guessed and the shoe not tried on. This is of course to be expected and could be easily remedied. In only 10 cases out of 1,024 was specialist orthopaedic opinion considered necessary, and in eight of these no treatment was needed.

The lesson of these surveys seems to be that it is too early yet to be dogmatic about many of the issues raised; there is still room for honest divergence of opinion. To insist, as some do, on the adoption of a particular form of footwear because of an unsubstantiated theory may merely be an example of the blind leading the blind.

HYPOPHYSECTOMY BY IRRADIATION

Various methods of destroying the pituitary by radiation have been under trial during the past few years in an attempt to provide a simple method of palliation, less exacting than surgical endocrine ablation, for the patient with advanced hormone-dependent cancer. The problems which confront the therapist are the small size, depth from the surface, and radio-resistance of the normal hypophysis, and its proximity to vital nervous tissue.

External radiation, delivered by conventional apparatus[1] and the betatron,[2] cannot selectively destroy the pituitary, but a collimated beam of 340 MeV protons, generated by a synchrocyclotron and delivered by a multiple-port rotational technique, has been used with success for this purpose by C. A. Tobias and his colleagues in Berkeley, California. These workers have recently reported their results in 26 patients with breast cancer.[3] Only four patients had arrest or regression of disease for over three months, but half of the 26 had previously been treated by adrenalectomy and oophorectomy and could not be expected to benefit further. The Berkeley group have also treated 50 patients by irradiation of the pituitary with 900 MeV alpha particles.[4]

Those without access to a cyclotron have taken the source of radiation to the pituitary gland by implanting radioactive rods or pellets into the sella turcica by a transcranial approach[5] or by transnasal[6 7] or transphenoidal cannulation.[8] Suitable materials should emit radiation of high energy, but limited range, have a short half-life, and be available in reasonably solid form. As the gamma emissions from radon[9–12] and radioactive gold (^{198}Au)[13–17] penetrate beyond the pituitary and deliver significant amounts of radiation to surrounding structures the use of these sources has generally been abandoned. Emulsions of radioactive chromic phosphate (^{32}P),[18–20] although possessing suitable radiation properties, also endanger the hypothalamic structures by diffusion.

Irradiated yttrium oxide (^{90}Y) satisfies the above requirements, since this isotope emits only beta particles of energy 2.2 MeV, penetrating to not more than 1 cm. in tissue, and has a half-life of 64 hours. The suitability of this material for implantation into the sella was first investigated by T. Rasmussen and his colleagues in the University of Chicago,[21] and

1 Kelly, K. H., *et al.*, *J. nat. Cancer Inst.*, 1951, **11**, 967.
2 Nickson, J. J., in *Hypophysectomy*, 1957, Springfield, Ill. (p. 127).
3 Tobias, C. A., *et al.*, *Cancer Res.*, 1958, **18**, 121.
4 —— personal communication to A. P. M. Forrest *et al.*[10]
5 Pattison, A. R. D., and Swan, W. G. A., *Lancet*, 1938, **1**, 1265.
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J. P. Evans, W. A. Kelly, and P. V. Harper from there now report their experience in 44 patients with advanced malignant conditions (31 of breast origin) in whom up to 16 0.5 mC pellets of ^{90}Y were implanted by transfrontal craniotomy.[22] This procedure was not without complication, and one patient developed optic atrophy, twelve extraocular palsies, seven damage to the frontal lobes, and five cerebrospinal rhinorrhoea. The operative mortality (18.1%) compares unfavourably with that recently reported for surgical hypophysectomy by O. H. Pearson and B. S. Ray.[23] The extent of destruction of the pituitary after transcranial ^{90}Y implantation, assessed histologically at necropsy in 22 patients, varied from 20–95%, while regression of breast cancer occurred in only 3, and arrest in a further 8 of the 31 patients treated. These results clearly show that if the skull is to be opened a more effective procedure is to remove the hypophysis surgically and destroy any remnants with either Zenker's solution[23] or radioactive material.[24 25]

Introducing rods, pellets, or spheres of ^{90}Y into the pituitary fossa by transnasal cannulation is a relatively simple procedure.[14 26–31] Extrasellar radiation effects are rare after this method of treatment, but about one-fifth of patients develop cerebrospinal rhinorrhoea with the risk of subsequent meningitis. Histological studies reported by M. E. S. Mahmoud[32] have shown that the diaphragma sellae normally seals off the pituitary fossa from the subarachnoid space, and the association between high-placed rods and rhinorrhoea[10 31 33 34] suggests that necrosis of this membrane is the main factor responsible for the leak. While this can be prevented by inserting small tantalum screws in the drill holes,[17] accurate placing of the ^{90}Y sources at a safe distance from the diaphragma is of prime importance.[31] It is not easy to place free rods or pellets of ^{90}Y regularly in an optimum position, and this also accounts for the low incidence of complete destruction of the gland after their implantation (11 of 46 cases[10 28 29 35 36]).

These difficulties are largely overcome by the method of screw-implantation described by A. P. M. Forrest, D. W. Blair, and J. M. Valentine in Glasgow.[37] By this method an yttrium rod is fixed in the centre of each half of the gland, and the precision with which they can be placed has resulted in fewer complications and consistent 98–100% destruction.[9 10]

These various methods of pituitary irradiation are still experimental and cannot yet be advocated as a simple alternative to surgical hypophysectomy. In the hands of general surgeons bilateral adrenalectomy and oophorectomy still has much to commend it as a method of bringing welcome palliation to the patient with advanced breast cancer.

TEACHING OF DERMATOLOGY

It is a common complaint by young general practitioners that their clinical training failed to prepare them for the large amount of dermatological work they have to undertake as family doctors. The Committee on Dermatology of the Royal College of Physicians, under the chairmanship of Professor J. T. Ingram, recommends better opportunities for general practitioners to receive postgraduate instruction in dermatology. Many young practitioners, the committee's report[1] states, would welcome an appointment as clinical assistant in a dermatological department, where they could attend for, say, one session a week for six months. The committee also thought there was a need for refresher courses for consultant dermatologists, who should, if possible, always be associated with their university centre. There are not enough dermatologists, particularly in the provinces, to deal efficiently with all the patients that are referred to hospital, and the report states that a plan for the better distribution and organization of dermatological services is overdue. Those concerned about the multiplication of diplomas will be relieved to learn that the institution of a special qualification or diploma in dermatology is not thought to be necessary.

As to undergraduate teaching, the committee does not think that dermatology has yet played its proper part in preclinical and clinical education. There are opportunities for the dermatologist to co-operate in the teaching of biology and physiology as well as in the teaching of medicine. The report advocates that students should have a clerkship in dermatology early in their clinical course, and that this might be shared with another branch of study, preferably general medicine. In the committee's view there should always be a dermatological question in the final medical paper.

CONSTITUENTS OF POLIO VACCINES

The programme of vaccination against poliomyelitis is so well advanced in Great Britain that the Minister of Health was able to announce recently an extension of the scheme to include adults up to 40 years old.[2] It is too early to assess with certainty the result of the programme so far, but at least the incidence of paralytic disease in 1959 was the lowest for many years.

The vaccine manufactured in Great Britain is made from formalin-inactivated suspensions of the three types of poliomyelitis virus grown in cultures of monkey kidney tissue. The attenuated Brunenders strain is used for the type 1 component in preference to the Mahoney strain favoured in Canada and the United States.

[1] Royal College of Physicians of London. Committee on Dermatology Report. January, 1960.
[2] *Brit. med. J.*, 1960, **1**, 436.

MEF 1 and Saukett are used for the type 2 and 3 components in vaccine made in Britain and in North America.

Up to 200 units per ml. each of penicillin and streptomycin are used for controlling contamination during the manufacturing process, and small amounts of them, or their degradation products, are present in the final product. Penicillin itself is usually at an undetectable level, as it is destroyed by the process of virus inactivation, while the amount of streptomycin varies from 10 to 50 units per ml. Benzethonium chloride, or thiomersal in conjunction with versene, is used as a preservative. The pink or orange colour of vaccine is due to dilute phenol red, which is added, as a *p*H indicator, to the tissue culture during manufacture.

Vaccine will retain its potency for at least twelve months if kept at 4° C. or thereabouts. A day or two at room temperature is not deleterious, but vaccine should not be kept out of a refrigerator longer than is necessary.

Reactions are very rare after the injection of poliomyelitis vaccine, which usually causes no discomfort to the recipient. Erythematous and urticarial rashes, headache, malaise, and bronchospasm have been reported, some of which are considered to be due to residual penicillin or its degradation products in the vaccine. Because of this some vaccine is being produced without penicillin, polymyxin being used instead. A history of allergy or mild sensitivity to penicillin is no contraindication to the use of poliomyelitis vaccine. If severe reactions have occurred after administration of penicillin, vaccine without penicillin is preferable.

Vacination can be carried out throughout the year in all subjects except perhaps at the height of a severe epidemic of poliomyelitis. The evidence that injection of the vaccine may provoke paralysis is conflicting; if it does do so, the risk is in any case so low that it is worth taking. Patients with acute nephritis should not be inoculated until the initial phase has passed. Vaccine can be given effectively to people of all ages, but in babies below 6 months of age the production of antibody is poorer than in older subjects. However, these babies can be protected by placentally transmitted maternal antibodies. The mother should be immunized during pregnancy both for this reason and because pregnancy increases susceptibility to paralysis.

The initial inoculation schedule recommended is two doses 4–6 weeks apart, followed 6–12 months later by a third booster dose. With the vaccine available over the last few years, and 1 ml. being used for each dose, this schedule should give protection in 70–90% of individuals for some years, adults and adolescents probably being less well immunized than children. To increase the chances of good immunization in special cases, a fourth injection should be given 6–12 months after the third dose or the dose raised to 1.5 or 2 ml., especially in older subjects.

Most of the British vaccine issued recently has been of higher potency, especially against the most paralytogenic type 1 virus, than that previously available, including those vaccines imported from overseas. With further increases in antigenicity it should be possible with three doses to give all subjects as long a period of immunity as that obtained with tetanus and diphtheria prophylactics.

AN INTRACARDIAC PACE-MAKER

The technique of cardiac catheterization, first introduced by W. Forssmann in 1929[1]—for which he was awarded a Nobel prize in 1956—has largely been used for diagnostic purposes. Gas analysis of intracardiac blood samples, measurements of pressure and of dye dilution, intracardiac electrocardiograms, and local angiocardiography are all performed with its help. Now a therapeutic use of the cardiac catheter is suggested—namely, to deliver electric shocks directly to the endocardium and thus obtain an intracardiac pace-maker. S. Furman and J. B. Schwedel, after testing the intracardiac pace-maker in the dog, have recently used it successfully in the treatment of two patients with Stokes–Adams disease.[2]

A Cournand electrode catheter, with no lumen, but bearing a copper wire with an exposed metallic tip, was passed via the median basilic vein into the right side of the heart under radiographic control. The tip of the catheter was placed in the right ventricle. The ground electrode was a bare copper wire, silver-covered and embedded subcutaneously in the left side of the chest. Stimulation was then begun using between 1.5 and 3 volts, and it was found that complete control of the heart rate could be maintained for long periods using only these small voltages. In one patient it was thought necessary to maintain an artificial heart beat in this way for 96 days, during which time sensitivity to stimulation remained constant and thrombophlebitis was prevented by the use of anticoagulants. After the catheter was finally withdrawn, no further periods of asystole occurred and the patient remained well.

In the treatment of Stokes–Adams disease the advantages of an intracardiac pace-maker, as opposed to an external pace-maker applied to the chest wall,[3] appear to be considerable and may eventually be found to outweigh the drawbacks and possible complications. The external pace-maker is painful, because it causes strong contractions of the muscles of the chest wall with each artificially induced heart beat. The intracardiac pace-maker, on the other hand, is painless, the patient being hardly aware apparently of the stimulation itself. During the period of treatment sedation is therefore no longer required and the patient may be ambulant, using a long length of flex plugged into the mains supply; the pace-maker itself is pushed along by the patient on a small table on wheels. It would seem possible that the principle of direct endocardial stimulation of the heart may be found to have other useful applications in the field of cardiac resuscitation, which was discussed in these columns last week.[4]

[1] Forssmann, W., *Klin. Wschr.*, 1929, **8**, 2085.
[2] Furman, S., and Schwedel, J. B., *New Engl. J. Med.*, 1959, **261**, 943.
[3] Zoll, P. M., Paul, M. H., Linenthal, A. J., Norman, L. R., and Gibson, W., *Circulation*, 1956, **14**, 745.
[4] *Brit. med. J.*, 1960, **1**, 40.
[5] Ross, J. K., and Harkins, G. A., *Lancet*, 1959, **2**, 1109.

When heart block develops unexpectedly after open heart surgery and electrodes have not been left in contact with the heart, this method offers an alternative means of applying a direct pace-maker to the heart. Another method recently described is percutaneous ventricular puncture. J. K. Ross and G. A. Harkins[5] report the placing of an electrode in contact with the myocardium.

FEMALE CARRIERS OF HAEMOPHILIA

Many studies have shown haemophilia is inherited through a sex-linked recessive gene. It therefore primarily affects males, and the gene passes to them through clinically normal females. The recognition of the female carrier would provide some possibility of reducing the number of affected persons. A woman who knew for certain that she was a carrier of haemophilia might hesitate to produce a family and risk perpetuating the disease, with the misery and worry that it entails.

Many attempts to recognize the carrier from clinical and laboratory evidence have been made, and the claims for their reliability have been varied. Some female carriers of haemophilia undoubtedly bleed excessively, and the blood of some of them gives abnormal results with various laboratory tests. Most investigators would agree so far; the disagreement concerns the proportion of carriers in whose blood an abnormality can be found. If half the carriers give abnormal results and half normal, then a normal result would carry no weight in convincing a potential carrier of haemophilia that it would be safe to embark on a family. The normal result merely somewhat reduces the odds against the arrival of haemophilic children.

In a recent study I. M. Nilsson and her colleagues[1] have reinvestigated this problem. They used two techniques for the study of the level of antihaemophilic globulin (A.H.G.) in the blood of carriers of haemophilia. One method was an assay based on the thromboplastin-generation test. The second was based on the correction of the calcium clotting time of known haemophilic plasma. The second method would be expected to be much influenced by technical factors and therefore difficult to reproduce. Yet by this method 13 out of 13 proved carriers in the child-bearing age gave abnormal results, whereas only 6 out of 9 gave abnormal results with the thromboplastin generation test. In all, 75% of the tests on the females in haemophilic families studied gave abnormal results by the calcium clotting-time method, whereas only 50% of abnormal results were obtained with the thromboplastin-generation test. The reason why the calcium clotting-time method was superior is at present obscure. The tests need repeating in other parts of the world, since females in haemophilic families may more frequently have abnormal blood in Sweden than elsewhere. Nilsson and her colleagues give full details of the collection of blood samples for the calcium clotting-time test, and by reading several publications a rough outline of the method can be pieced together. But it is unfortunate that all the details necessary to achieve reproducible results are not available, for lack of detailed technical instructions will hamper the proper repetition of these observations by other workers.

[1] Nilsson, I. M., Blombäck, M., Thilén, A., and Francken, I. V., *Acta med. scand.*, 1959, **165**, 357.

THE TORQUAY MEETING

This year's Annual Meeting, to be held at Torquay, will be rather earlier than usual. The A.R.M. will start on Thursday, June 16, and the last of the scientific sessions will be on Friday, June 24. The provisional programme is published in this week's *Supplement*, and a list of hotels is given to help those who have not yet booked their accommodation.

Torquay in June should be one of the most agreeable spots in the British Isles, and the organizers of the meeting have done their best to devise a scientific programme which will compete with the natural attractions of South Devon. The symposium on "The Contribution of Medicine to Efficiency in Sport" is particularly timely, as it will be taking place just a few weeks before the Olympic Games in Rome: with Sir Arthur Porritt, the President-elect of the B.M.A. and himself an athlete with a distinguished record at earlier Olympic Games, in the chair and with a panel of expert speakers, this is sure to be an informative and interesting discussion. The three major Sections have each chosen an arresting subject for one of their meetings—"Medical Treatment as a Cause of Disease" by the Section of Medicine, "Economic Aspects of Surgical Treatment" by the Section of Surgery, and "Sex Determination" by the Section of Obstetrics and Gynaecology. The Section of General Practice, too, should have a lively morning discussing the question, "Have Health Centres Justified Themselves?"

DRUGS FOR PRIVATE PATIENTS

Parliament and Press are at last waking up to the fact that for twelve years an injustice has been done to those who wish to take advantage of one of the four principal parts of the National Health Service. They were promised in the White Paper of 1946 that: "All the Service, or any part of it, is to be available to everyone in England and Wales." Ever since 1948 the B.M.A. has urged, year after year, that, according to this promise, private patients should be able to have their drugs on the same terms as N.H.S. patients. The Conservative Party declared long ago that this was not contrary to their policy. It is therefore most encouraging to see that a growing number of Conservative M.P.s have added their names to Mr. A. Marlowe's motion in favour of this (see p. 509). And it is not surprising to find a counter-move to this by Labour M.P.s on the initiative of Mr. L. Pavitt, recently national organizer of the Medical Practitioners' Union. The B.M.A. has removed the principal objection to the granting of this right by agreeing that doctors with private patients should submit to control in respect of N.H.S. drugs prescribed for them.

Drug Treatment of Disease

CORTICOSTEROIDS IN TREATMENT OF RHEUMATIC DISORDERS

BY

F. DUDLEY HART, M.D., F.R.C.P.

Westminster Hospital, London

When in 1949 Hench demonstrated the effect of large doses of cortisone in patients with rheumatoid arthritis, there were high hopes that a true "antirheumatic" drug had been born. It became rapidly apparent that this new substance was not curative and had no lasting effect on the disease process, relapse occurring soon after it was discontinued. Hench and his clinical colleagues, Slocumb and Polley, were careful to avoid the word "cure" and emphasized that the drug only suppressed the inflammatory and certain other features of the disorder.

Though the word "antirheumatic" has been widely used since then in connexion with these and other drugs, it means singularly little, and can mean little, until we know more of the aetiology of these disorders. Relief of pain and reduction in tissue swelling occurs in a number of diseases other than rheumatoid arthritis. The corticosteroids cannot truly be said to be specifically "antirheumatic."

Corticotrophin and cortisone and its analogues are used to-day in selected cases of rheumatoid arthritis, rheumatic fever, gout, Reiter's (Brodie's) disease, ankylosing spondylitis, psoriatic arthropathy, the arthropathy associated with ulcerative colitis, and the so-called "pararheumatic" disorders—systemic (disseminated) lupus erythematosus, polyarteritis nodosa, scleroderma, dermatomyositis, and cranial arteritis. In all these disorders they produce symptomatic relief in varying degree. The indications for their use and the contraindications to it in these different disorders are in some measure a matter of individual opinion, but certain facts have been learnt in the hard school of experience in the six or seven years that these substances have been used in Great Britain.

In general it may be said that it is far easier to start steroid therapy than to stop it. The early improvement noted on such therapy in any of these disorders may be maintained for months or years, but, unless natural remission sets in, all too often so-called "side" effects become more apparent as the drug's beneficial effects become less so, and with the passage of time one finds oneself treating a state of hypercortisonism induced by therapy in addition to a partly suppressed arthritic process. The moon-faced somewhat obese patient with striae and other signs of hypercortisonism, but still with active rheumatoid arthritis, is all too well known to most of us.

Available Corticosteroids

At present there are available for treatment of the rheumatic disorders:

Corticotrophin (hospitals only)
Cortisone
Hydrocortisone (cortisol)
Prednisone
Prednisolone
Triamcinolone
Methyl prednisolone
Dexamethasone

With the exception of corticotrophin, which is given by intramuscular injection, the usual route of administration is by mouth. The tablets in common use are: 25 mg. cortisone acetate, 20 mg. cortisol, 5 mg. prednisone and prednisolone, 4 mg. triamcinolone and methyl prednisolone, and 0.5 mg. dexamethasone. These doses are very roughly equivalent and exert approximately the same action on inflamed tissues except for dexamethasone, where the equivalent dose is probably 0.75–1.0 mg.

For continued day-to-day long-term suppressive therapy in rheumatoid arthritis it is considered safer by most clinicians not to exceed 3 tablets as a regular daily dose with the older preparations—that is, cortisone 75 mg., cortisol 60 mg., prednisolone and prednisone 15 mg. Though larger dosage may be permissible over short periods, continued therapy for weeks or months will in time produce undesirable so-called side-effects even at this conservative dose level. For this reason the daily dose should be kept as low as is reasonably possible.

Trial and Error

What are the essential differences in the orally administered corticosteroids and when should one be given and when another? A good deal of trial and error is required. What suits one patient admirably may not suit another so well. As we have noted above, the relative potency of the different substances is reflected, except with dexamethasone, in the strength of the tablet; 25 mg. of cortisone equals 20 mg. of cortisol, 5 mg. of prednisone or prednisolone, 4 mg. of triamcinolone or methyl prednisolone, and about 0.85 mg. of dexamethasone. There is no particular reason for giving a smaller dose of a stronger substance if the overall effect is virtually the same.

The practical advantages of prednisone, prednisolone, triamcinolone, methyl prednisolone, and dexamethasone are that they cause less retention of sodium, and therefore of water, than do cortisone or cortisol. Moon face, gastro-intestinal disturbances, mental upsets, osteoporosis, and other features of therapeutic Cushing's syndrome occur, however, with all these substances, and we have not been impressed to date by any significant difference in the incidence of these side-effects with the different steroids. Claims of diminished incidence of side-effects of one sort or another are made for each new steroid as it arrives, but clinical experience usually shows up such claims as wanting in whole or in part.

Corticotrophin deserves a short paragraph to itself. It is at present available only to hospitals and treatment centres and cannot be prescribed on form E.C.10. It may be given intravenously to stimulate adrenocortical secretion, but is usually administered by the intramuscular route, the long-acting form being the preparation most widely used. Some workers claim that gastric symptoms are less severe with

corticotrophin than with orally administered steroids, but nevertheless they do occur. Peptic ulceration may be aggravated and the patient suffer perforation or bleeding. When the ordinary preparation is given by intravenous injection, or by intramuscular injection of 10–15 units every hour for 4–6 injections, a therapeutic effect is obtained within a few hours. When the "retard" form is given intramuscularly, therapeutic effects are not usually apparent for some 24 hours or more. Drawbacks to the use of corticotrophin are that it must be given parenterally, and that it occasionally causes allergic local reactions. In such cases its therapeutic efficacy is much diminished, and patients with rheumatoid arthritis, for instance, experience a rapid return of symptoms. In its early days (1950–2) the strength of corticotrophin varied in different batches, so that considerable variations in the patient's condition occurred on a constant dosage. This is now much less of a problem. To-day, also, one does not see the deep-brown pigmentation owing to contamination of preparations of corticotrophin with M.S.H. (melanocyte-stimulating hormone) which large doses sometimes caused in the early period.

Mode of Action

Given orally or by intramuscular or intra-articular injection, the various steroids exert their action in the inflammatory rheumatic disorders by increasing vascular stability, lessening inflammatory exudation and so reducing swelling, stiffness, and discomfort, and increasing the range of movement of a joint. There is an increased sense of well-being in many cases and an increased appetite, energy, and drive, but with triamcinolone appetite tends to diminish and the patient to lose weight. The sedimentation rate tends to fall to, or towards, the normal range and the blood picture to improve.

The exact mode, or modes, of action of these substances is still imperfectly understood, and when treating a rheumatic disorder it is as well to keep in mind the fact that all the body systems may be affected to some degree by steroid therapy. One is altering the tissues not only of the inflamed joints but of the patient in his entirety.

Hazards of Corticosteroid Therapy

These are well known and there is no need to dilate on them. Three, however, are of particular importance in the rheumatic disorders.

1. *Gastric Irritation.*—This manifests as dyspepsia with or without peptic ulceration, and has seemed to be more common in the rheumatoid group of patients than in any other. These patients, unlike, for instance, those with ulcerative colitis or asthma, usually take a regular additional daily dose of aspirin, which may also produce gastric symptoms. Gastric ulceration is more common than duodenal, suggesting the possibility of a local concentrated action by the tablet on the gastric mucosa. Many patients' dyspeptic symptoms lessen appreciably when tablets are crushed and taken with food or drink, followed by an antacid.

2. *Withdrawal Syndrome.*—On a regular daily dose of a corticosteroid, the patient's own adrenal glands become functionally depressed. In the face of any serious form of stress, the dose must therefore be increased and never reduced or discontinued. Patients should be told of this fact, for there is a tendency for both patient and doctor to reduce or stop treatment at the onset of, for example, acute gastro-enteritis. To combat this we issue cards to all patients on steroid therapy stating the dose and preparation, and emphasizing the fact that increased stress, whether it be acute infection or an emergency operation, calls for increased dosage. To cover a major abdominal operation, for instance, some 300 mg. or more of cortisol or cortisone is usually given. Sudden stopping or major reduction of dosage in rheumatoid arthritis in the face of stress may be followed not only by signs of adrenal exhaustion and exacerbation of the arthritis, but occasionally by peripheral neuritis, probably a sign of a flare-up of a previously suppressed arteritis. The risk of impaired healing after surgery can be ignored in practice, for normal healing of tissues occurs on full dosage; the withdrawal syndrome is a far bigger and more real hazard.

3. *Osteoporosis and Fractures.*—In rheumatoid arthritis there is often some osteoporosis, partly the result of the disease and partly due to relative immobility. As corticosteroids also cause osteoporosis, the incidence of severe osteoporosis and fractures is higher at the higher dose levels and in the more crippled and disabled patients who cannot get about. For this reason prolonged steroid therapy should never be given to bed-ridden or chair-fast subjects. Particular attention should be given to so-called pleurisy pains, which may be due to fractured ribs, and to backaches, which may be due to crush fractures of vertebral bodies.

Intra-articular Injections

Hydrocortisone acetate, hydrocortisone or prednisolone tertiary butyl acetate, and prednisolone trimethyl acetate are now available for local intra-articular instillation. The effective dose ratio of the two is near unity; the 4 : 1 prednisolone : hydrocortisone ratio of efficacy when taken by mouth does not apply when these preparations are injected into the joints. Given intra-articularly, the effect milligram for milligram of these substances is very similar.

The duration of action is variable, even when the same substance is given into the same joint of the same patient in the same dose. Relief may be for a few hours only, for days, weeks, or very occasionally months. In the last case the local injection would appear to have broken a vicious cycle, the inflamed joint going into natural remission. These preparations may also be helpful in treating swollen osteo-arthritic joints, knees in particular. This is the only use of steroid treatment in degenerative joint disease, though recent controlled work (Miller *et al.*, 1958) has not shown it to be better than injections of inert substances, such as saline.

Rheumatic Fever

The steroids, it seems, have not replaced salicylates in the treatment of rheumatic fever. A joint co-operative study at twelve centres in the United States, Canada, and the United Kingdom four years ago (1955) found little difference in the cardiac condition one year after the completion of six weeks' treatment with cortisone, corticotrophin, or aspirin. There was no evidence that any of these three agents resulted in uniform termination of the disease, and on all forms of treatment some patients developed fresh manifestations of the disorder. Treatment with set doses of corticotrophin or cortisone resulted in more rapid control of certain acute manifestations, but there was an increased tendency for these to reappear on stopping therapy in the patients treated with steroids. Treatment with the hormones led to more rapid disappearance of rheumatic nodules and of soft apical systolic murmurs, but, as stated above, the cardiac

status after one year was virtually the same in all three treatment groups.

Illingworth *et al.* (1957), on the other hand, in a careful, controlled study, found that the cardiac status after one year was better in those treated with both cortisone and salicylate than with either substance alone. Cortisone alone, they concluded, was better than salicylates alone, but combined treatment gave the best results of all. Both these excellent papers should be read in their entirety. Prophylactic therapy aimed at eradicating the responsible haemolytic streptococcus appears to be producing early results.

Rheumatoid Arthritis

As has already been said, cortisone and its analogues do not cure, but merely suppress, the active features of the disease process. They also affect many other systems of the body to a greater or lesser degree and have a wide and variable effect on the patient himself as well as on his arthritis. It is important, therefore, to keep steroid therapy in reserve unless progress without it is progressively downhill and unsatisfactory in spite of a proper programme of adequate rest, analgesics, and splinting. Controlled trials by the joint committees of the Medical Research Council and Nuffield Foundation (1957a and b) in the early case, and of the Empire Rheumatism Council (1957) in the average later case, both trials covering periods of three years, have shown no real difference between those patients treated by aspirin and those by cortisone. Nevertheless, steroid therapy is still used fairly widely in the treatment of rheumatoid arthritis when other measures have not been adequate to prevent deterioration or arrest of the disease.

What are the contraindications and what are the indications for their use?

Almost absolute contraindications are peptic ulceration and psychosis; relative contraindications are diabetes mellitus and active tuberculosis. Steroid therapy may be used in these last two conditions provided adequate therapeutic control of them can be maintained. Steroid therapy is not indicated in the largely or entirely burnt out case, when residual changes only are present. It is essentially an anti-inflammatory agent for use when actual inflammatory changes are causing symptoms and signs. It is contraindicated in the bed-ridden or chair-fast case unless mobilization can be effected.

Indications are relative to each individual case. They include active inflammatory progressive disease affecting several or many joints when other measures have proved inadequate, and pseudo rheumatic fever, with high fever and systemic upset, with the patient deteriorating on orthodox therapeutic measures.

Steroid therapy should never be begun because the subject cannot rest enough or will not take sufficient time off work. Such cases are very difficult to treat; for economic or personal reasons they feel they must work on. Steroid therapy merely allows these patients to injure their affected joints more by doing too much at work, and it is these subjects who so often show the worst therapeutic results and the major complications of such therapy. Cortisone and its analogues must never be given when the patient will not co-operate by resting properly; they are supplementary to such general measures and do not replace them.

Dosage for Rheumatoid Arthritis

The regular daily dose should be the smallest which enables the patient to get through his restricted day with the minimum of disability and pain. The dose should occasionally be tentatively reduced to find out if the disease has subsided or become less active and to see if a smaller dose can be effectively given. Such dose reduction should be slow and gradual, half a tablet at a time, and the next reduction should not be made until a further three weeks or more has elapsed.

Daily doses above 75 mg. of cortisone, 60 mg. of cortisol, 15 mg. of prednisolone or prednisone, 12 mg. of triamcinolone, or 2.5 mg. of dexamethasone should not be given over long periods. If higher dosage than this is required for more than a few weeks it is wiser to discontinue steroid therapy gradually, for unwanted effects will soon appear, and the physician may find himself treating active rheumatoid arthritis in a case of Cushing's disease, often with superadded dyspepsia.

Gout

Corticosteroids may be used to treat the acute episode when colchicine or phenylbutazone prove unsatisfactory. They are not suitable as suppressive or uricosuric agents in this disease.

The usual practice is to give a short course of some six or seven days, the dose being reduced daily; colchicine, ½ mg. once or twice a day, is continued for a further ten days subsequently to prevent "rebound" attacks on withdrawing steroid therapy. The initial dose varies according to individual requirements, but 60 units of corticotrophin, 30–40 mg. of prednisone or prednisolone, or equivalent doses of the other substances will probably be necessary on the first day, the dose being then reduced daily by one tablet (5 mg.) or 10 units. Higher dosage may be necessary in some cases, and in very acute or resistant cases intravenous or repeated intramuscular injections of corticotrophin.

Polyarteritis Nodosa and Systemic Lupus Erythematosus

In these more serious conditions the same dosage rules apply as with rheumatoid arthritis, but higher dosage is permissible and occasionally absolutely necessary. At high dosage a close watch must be kept for signs of intercurrent infection and suitable antibiotic therapy rapidly instituted at the first sign of it. There is no evidence that the natural history of these disorders is fundamentally altered by steroid therapy, and renal disease in the later stages is unaffected. Dosage, as with rheumatoid arthritis, should be as low as is compatible with a reasonable existence. The dangers of sudden withdrawal or too rapid reduction of dose are greater than with rheumatoid arthritis, new visceral and polyneuritic manifestations rapidly appearing with high fever and an increase in circulating L.E. cells. With all its drawbacks, steroid therapy is the best at present available in the symptomatic control of these conditions.

Cranial (Temporal) Arteritis

In this painful febrile disorder, steroid therapy relieves the typical bitemporal headache rapidly and effectively in most cases, and diminishes or eliminates the fever and general malaise. Blindness, however, may

still occur despite a dose which effectively relieves all other symptoms, but it may be that, in some at least of such cases, therapy has been started too late or in too low a dosage. Low-grade fever and diffuse aches and pains may persist in some of these, usually elderly, patients, with raised sedimentation rate, for some weeks or months subsequently. It may be due to a diffuse residual subacute arteritis, which often responds very satisfactorily to small doses of steroids.

Dermatomyositis and Scleroderma

In many cases steroid therapy may cause some symptomatic improvement in these disorders, but all too often the improvement wears off after some months of treatment. Steroid therapy will not prevent progression of the disease or deterioration in the patient's condition, and is not as effective in these disorders as in the others mentioned.

Conclusions

Steroid therapy suppresses symptoms but is not curative. So-called "side" effects—that is, features of Cushing's syndrome—may be expected if one gives adrenocortical hormones in pharmacological rather than physiological doses to patients with intact adrenal glands. Dyspepsia, with or without peptic ulceration, is an even greater drawback to this form of therapy. There is relatively little to choose between the various steroids available for therapy; some patients benefit more with one, other patients with another. We have now quite a range of effective substances to turn to, all giving much the same side-effects, though the newer ones are preferable if the patient becomes loaded with salt and water. It is important to remember that the patient as a whole, as well as his joints and ligaments, is affected by this form of hormone therapy: the withdrawal syndrome is a not infrequent unpleasant reminder of this fact.

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Letter from Sir Alan Herbert to the "Daily Telegraph" (*January* 30): "Sir,—I hope that your great paper will refuse to print the half-baked and meaningless word 'breathalyzer' again. What idiot invented it? May I inform him that there is no verb 'alyse' and no noun 'alyser' or 'alysis'? 'Breath-analyser' would be harmless but long. Why not 'breath-tester'? A sports correspondent in another paper writes about a 'heartometer,' which recorded the action of a runner's heart. If 'cardiometer' is too much for his readers, why not 'heartmeter' or 'heart-recorder'? And why that fancy 'o'? What is a 'hearto'? Any Briton is entitled to despise Latin and Greek, especially if he has not had the opportunity to study them. But he should modestly refrain from inventing and spreading crazy words with bits of Latin and Greek in them which he does not understand."

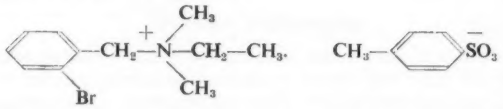
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Bretylium Tosylate

"Darenthin" (Burroughs Wellcome).

Chemistry.—This is N-*O*-bromobenzyl-N-ethyl-N:N-dimethyl-ammonium *p*-toluenesulphonate, and has the following structural formula:



Pharmacology.—Bretylium tosylate selectively blocks transmission in the postganglionic adrenergic sympathetic autonomic nerves and prevents the release of adrenaline and noradrenaline at the nerve endings. It is therefore a peripheral vasodilator and is advocated for the control of hypertension. It does not reduce, but potentiates, the effects of injected adrenaline or noradrenaline, and it does not prevent the release of these amines from the suprarenal medulla, whose nerve supply is cholinergic. Thus it would not be expected to control the hypertension of phaeochromocytoma, which may indeed actually increase if bretylium is given.

Therapy.—Though it does not attack the primary causes of hypertensive disease, bretylium has a site of action hitherto unavailable for clinical use. The chief importance of a hypotensive drug with a new site of action confined to the sympathetic system is that it may offer effective control of the blood-pressure with fewer side-effects than the drugs hitherto in general use, all of which have obvious and often serious disadvantages.

Bretylium can control hypertension in man, but sometimes very large doses are needed, possibly owing to erratic absorption from the intestine. In cases that are not controlled by 2–3 g. a day it is probably best to combine the bretylium with another hypotensive drug such as pempidine, chlorothiazide, or reserpine, which can then probably be used in small enough dose to avoid serious side-effects. The drug is supplied in scored, coated 200-mg. tablets. The initial dose may be 100 mg. orally three times a day, increased by 100–200 mg. per dose daily. Bretylium can also be given intravenously or intramuscularly, but no data on its clinical utility by these routes are yet available.

Some tolerance may occur. Patients with slightly defective renal function have been treated without mishap, but caution is obviously essential if the drug is given to those with severe renal failure. The supine blood-pressure is often but little reduced, and, as with other hypotensive drugs, the fall is mainly seen in the erect posture.

Side-effects.—In therapeutic doses bretylium does not block autonomic ganglia, and so patients are spared the often intolerable parasympathetic side-effects of ganglion-blocking drugs—constipation, dry mouth, blurred vision, impotence, etc. As with all potent hypotensive drugs, postural hypotension may be severe, and among other side-effects noted there have been diarrhoea, parotid pain, failure of ejaculation, and blocked nose.

It is clear that the introduction of bretylium marks an advance in the drug control of hypertension, but it, like other drugs, can fail, and it may in some cases give best results when used in combination. Its site of action is new and the drug has the advantage of more selective action than ganglion-blocking agents, whose effective use is inevitably accompanied by very tiresome side-effects.

N.H.S. Basic Price.—100 tabs. 200 mg., 35s.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Management of Acute Myocardial Infarction

SIR,—Dr. A. Rae Gilchrist, in his invaluable paper in your issue of January 23 (p. 215), draws proper attention to the use of pressor drugs to counteract shock, but, in this context, fails to mention the most valuable of them all. He recommends cortisone for its power to reduce local oedema and in the treatment of complete heart-block resulting from a myocardial infarct invading the ventricular septum. His Fig. 6 dramatically demonstrates its effect. But in this case it was administered after 20 days.

For some 10 years it has been my practice to give cortisone and latterly hydrocortisone in severe shock as early as possible after the occurrence of infarction, and I have seen patients unconscious, pulseless, and with blood-pressures suggestive of imminent death recovering in a matter of hours. I cannot claim to have made a controlled experiment, but I am sure that other physicians who have adopted this treatment—it is so rational that many others must have tried it—will have formed the opinion that on occasions it has been life-saving.

May I add a minor, perhaps captious, criticism, maybe of you, Sir, rather than of Dr. Gilchrist? He uses "g." to represent gramme and "gr." to represent grain. This, as the *British National Formulary* points out, may lead to confusion. The proper abbreviation of gramme is "G."—I am, etc.,

London, W.1. RAYMOND GREENE.

*** The abbreviation of gramme recommended by the British Standards Institution is g, without a point after it. The *Biochemical Journal* (in "Suggestions to Authors," 1957) recommends g. with a point. (There is something to be said for using a point to distinguish an abbreviation from a contraction: J. or Jnl for journal.) Capital G is an abbreviation for gauss. As an antidote to doctors' handwriting the *British National Formulary* recommends G. for gramme. With complete adoption of the metric system, this confusion would be avoided.—ED., *B.M.J.*

Cold Injury in the Newborn

SIR,—Dr. B. D. Bower and his colleagues (*Journal*, January 30, p. 303) are to be congratulated in collecting so large a series of "cold babies," and for the very useful analysis of their observations. It is interesting to note that in 62% of the cases hypothermia was considered to be secondary to some other neonatal disorder. The remainder were labelled "primary cold injury," but no very definite clinical picture is given of this group, and only two of the listed features, oedema and immobility, occur in more than half the cases. It would have been interesting to have learnt how the two groups differed both clinically and in respect of their environmental history.

Although no one would deny that a cold environment is an important aetiological factor in producing hypothermia, one wonders whether there may not be others as yet unknown but perhaps more important. It is probable that many babies are exposed to a cold environment yet never develop hypothermia, while others that do so have always been kept in the warm. Are these the same babies that may easily become overheated? It is obvious that we have yet much to learn about the mechanisms controlling an infant's body temperature. For these reasons the term "cold injury" seems to me to be too precise. Would it not be better to refer to all these cases as having "neonatal hypothermia," which might perhaps be further subdivided into "primary" and "secondary"?—I am, etc.,

Romsey. D. A. J. WILLIAMSON.

SIR,—In connexion with the article by Drs. B. D. Bower, Lilian F. Jones, and Mary M. Weeks on "Cold Injury in the Newborn" from the Birmingham Children's Hospital (*Journal*, January 30, p. 303), the following experience may be of some interest.

On the frosty night of January 11, 1959, I attended the second confinement of a Mrs. B. B. This was to take place in a bedroom heated by a small electric fire, and the window would not fully close. During a somewhat tardy first stage I ruptured the membranes when three fingers dilated, and one hour later at 5.30 a.m. she was delivered by a pupil midwife in my presence. This female infant weighed 8 lb. 12 oz. (3.97 kg.), and after weighing was quickly wrapped up and put in a pre-heated cot; in the meantime I had delivered the placenta.

She cried well at birth, but twenty minutes later it was noticed that she had grunting respirations, was expectorating a fine frothy mucus, and was peripherally slightly cyanosed. Her pharynx was again gently sucked out. She was not bathed or taken from the cot. Her condition did not change, so at 10 a.m. she was admitted to the Birmingham Children's Hospital under Dr. B. S. B. Wood with a tentative diagnosis of tracheo-oesophageal fistula. On admission her temperature was found to be 89° F. (31.7° C.). Radiograph of chest and "lipiodol" swallow showed no atresia and no cause for the respiratory distress. She was given oxygen for six hours, and then gradually weaned of it. As her temperature rose the child quickly improved, and was discharged on its third hospital day. Her subsequent development has been normal.

There was the minimal skin exposure to a cold room, and perhaps the inspiration of cold air is effective in producing this state.—I am, etc.,

Birmingham, 6. K. W. BREWSTER.

SIR,—The excellent paper on cold injury in the newborn infant by Dr. B. D. Bower *et al.* (*Journal*, January 30, p. 303) emphasized the need for low-reading thermometers, but ended on a depressed note in saying, "Unfortunately a low-reading thermometer will seldom be carried by the practitioner or midwife." In this area all midwives have for some time been supplied with low-reading thermometers, and the general practitioners advised to equip themselves similarly.—I am, etc.,

Plymouth. HUGH JOLLY.

Abortion and Ergometrine

SIR,—On several occasions the Obstetric Flying Squad of University College Hospital has been called to treat patients who have had severe haemorrhage during a miscarriage. Even in 1960 it is common to find that the general practitioner has failed to give ergometrine parenterally. Thus valuable time is lost and the patient may bleed so much that she becomes profoundly shocked.

Recently I have asked general practitioners why they have not given ergometrine by injection and the following have been the most recent replies:

"I do not carry ergometrine as abortions are uncommon."
"I gave liquid ergot by mouth, but she only vomited it."
"I did not think that ergometrine acted on the uterus early in pregnancy."

In the last case a district midwife wanted to give ergometrine but was actually prevented from doing so by the general practitioner. May I correct these misapprehensions? Miscarriages are common, especially towards the end of the first trimester when they are usually incomplete. Ergometrine given by mouth is an inefficient form of treatment but when given intravenously it is most effective. Surely there is a place in every general practitioner's bag for ergometrine ampoules. In cases of incomplete abortion 0.5 mg. should be given intravenously followed by a similar dose intramuscularly. In this way bleeding is reduced until the uterus has been evacuated.—I am, etc.,

University College Obstetric Hospital, London, W.C.1. J. R. SAUNDERS.

Fatal Diphtheria after Immunization

SIR,—In your issue of January 23 (p. 252) Drs. W. N. Dunnet, E. M. Schallibaum, and T. G. Scott describe a case of fatal diphtheria in a fully immunized child. The authors are to be congratulated on the thorough investigations they made into the clinical and other aspects of the case, though it is a thousand pities that they did not draw a little blood for antitoxin titration before administering the serum.

I am not sure that the title: "Fatal Diphtheria in the Fully Immunized Child" is quite justified from the data. Particulars of immunization and boosting, satisfactory in the vast majority of cases, are given, but I find no record that a successful result was confirmed, either after the primary course or the further dose of T.A.F., by means of either a Schick test or a blood antitoxin titration. Whatever course of immunization is given, a fraction of 1% of children does not respond adequately without further treatment; and, if the case in question was perchance one of these, it is quite likely that the booster dose some years later would not suffice to establish a protective amount of antitoxin or a good basal immunity. I would have preferred the title: "Fatal Diphtheria in a Child who had Received Immunizing Injections."

I note, too, that sections of the myocardium are described as showing changes consistent with *early* (my italics) toxic myocarditis. Yet toxic myocarditis takes precedence as the stated cause of death. Should not pneumonia perhaps have come first?

The case interests me greatly, as in the past I have myself met with one similar one, due to the mitis strain, in a fully immunized child, but this was happily not fatal.—I am, etc.,

Broadbridge Heath, Sussex. GUY BOUSFIELD.

Pitfalls in Chemotherapy of Tuberculosis

SIR,—The letter of Dr. Joanna M. Ward in the *Journal* of January 30 (p. 345) should not pass unchallenged with its suggestions that if a little trouble is taken in educating patients, P.A.S. (para-aminosalicylate) will be taken regularly and in the correct dosage. I can still remember my feeling of self-complacency on reading the paper written by Simpson[1] in 1956, in which he described a 24% default rate in taking P.A.S. among his patients. Such things did not happen in Bedford, where we took a good deal more trouble with our patients than the measures described by Dr. Ward. How wrong I was can be seen in a later investigation.

There is, however, one additional method to those reported which may reduce the default rate—a personal interview between a senior physician and a responsible relative of the patient, in which the need for regular medication is explained. My purpose in writing this letter is to stress that, until reliable evidence is produced to the contrary, Drs. Graham Poole and Peter Stradling (*Journal*, January 16, p. 161) are right in questioning the regularity with which patients will take P.A.S.—I am, etc.,

Chest Clinic, Bedford General Hospital, Bedford. N. WYNN-WILLIAMS.

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[1] Simpson, J. McD., *Tubercle (Lond.)*, 1956, **37**, 333.
[2] Wynn-Williams, N., and Arris, M., ibid., 1958, **39**, 138.

SIR,—Drs. Graham Poole and Peter Stradling (*Journal*, January 16, p. 161) have condemned calcium B-P.A.S. (calcium benzamidosalicylate) on the grounds that it fails to prevent the emergence of resistant strains of tubercle bacilli. I have been using calcium B-"pasinah" (calcium benzamidosalicylate with isoniazid) as the combination of choice with or without streptomycin since 1955. If this combination was as poor as is suggested by Drs. Poole and Stradling, one would expect a high proportion of patients excreting resistant tubercle bacilli in this particular area. In fact, I have 54 such patients, as against 32 of Dr. Stradling's, in an area twice the size and containing twice the number of patients on the tuberculosis register. Many of these became resistant before calcium B-P.A.S. was on the market.

From experience, therefore, I would suggest that there is little substance in their assertion that calcium B-P.A.S. is less effective than sodium P.A.S. in preventing the emergence of resistant strains.—I am, etc.,

J. A. KEEPING.

Paddington and Kensington Chest Clinic, London, W.2.

Postponement of Menstruation

SIR,—Concerning the excellent concise article by Dr. G. I. M. Swyer entitled "Progestogens and their Clinical Uses" which appeared in your *Journal* of January 2 (p. 48) and January 9 (p. 121), the following limited clinical trial to ascertain whether or not the oral progestogens would effectively postpone menstruation in women with regular normal cycles may be of some interest.

Fifteen subjects volunteered for this investigation. The ages varied between 21 and 30 years, and all had regular cycles between the limits of 24 and 32 days.

The norsteroid selected was norethisterone ("primolut N"), since clinical experience had revealed the effectiveness of this drug in arresting dysfunctional uterine bleeding and that it was the best tolerated of the new oral progestogens. Each volunteer was instructed to take one 5-mg. tablet three times a day, starting three days before the period was expected, and to continue (one tablet t.d.s.) to complete a course of eight days' duration. A proforma was issued to each participant for completion at the end of the trial.

Delay of Menstruation.—In seven of the subjects the period was delayed for seven days, in five the delay was

eight days, and in three 10 days. One subject with irregular periods commenced menstruating on the first day of taking the tablets, so was excluded from the series.

Effects of Menstrual Flow.—In 13 subjects the period was normal in amount and duration, while one experienced heavier loss than usual, although the duration was normal. One subject had a scanty loss protracted over eight days, her normal duration being five to six days.

Side-effects.—The majority did not complain of any side-effects. However, two subjects who usually suffered with abdominal heaviness, low backache, and some frequency of micturition a day or two before the onset of menstruation complained that this symptomatology had been prolonged to four or five days prior to the therapeutic "delayed" menstruation.

The evidence of this trial suggests, firstly, that the efficacy of progestogens in arresting dysfunctional uterine bleeding is related to their effectiveness in delaying "normal" menstruation. Secondly, that postponement of menstruation for any indication—for example, examinations, honeymoon, holidays—can be achieved with an optimum of certainty and a minimum of inconvenience by the use of norethisterone in the dosage scheme given above.—I am, etc.,

Westminster Hospital,
London, S.W.1. G. T. SMEDLEY.

Medico-legal Significance of the Fractured Skull

SIR,—I could not agree more with the opinion expressed by Mr. G. L. Alexander, Mr. D. G. Phillips, and Mr. A. Hulme (*Journal*, January 23, p. 274). It is, in fact, a justifiable indictment of the misuse of words in medical evidence—a habit which can lead to serious repercussions. Thus, as is correctly stressed, it is not the fracture which has caused the cerebral injury in many instances but the impact by or against the head. A good example is the deceleration injury so common in "knock downs."

It is the practice of my department to give as cause of death in such cases "cerebral contusion and haemorrhage *with* fractured skull." Although it is commonly incorrectly stated as "*due* to fractured skull" which may well give the impression that, if a fracture is not diagnosed, it is due to negligence. Whilst conversely, if not present, there can be no serious intracranial damage. Also it is not uncommon for *x*-ray examination to fail to show a fracture which can later be demonstrated at necropsy. This happens in the best neurosurgical units but does not influence a diagnosis of intracranial injury. It may even be that the reason so many fractured ribs are missed is because of the anxiety to show a fractured skull rather than how the impact occurred. Perhaps now that attention has been drawn to one example of inaccurate terminology, others may also be eliminated.—I am, etc.,

Department of Forensic Medicine,
The London Hospital Medical College,
London, E.1. FRANCIS CAMPS.

SIR,—I should very much like to second the proposal of Mr. G. L. Alexander, Mr. D. G. Phillips, and Mr. A. Hulme (*Journal*, January 23, p. 274) for a *démarche* by the medical profession in regard to the exaggerated medico-legal importance widely attached to fracture of the skull.

The time is long overdue for the general public to be impressed by the fact that brain injury is sometimes very serious even though the skull bones remain intact. Every housewife knows that she can break up a jelly which is still contained in its mould by shaking the mould vigorously, and the general public have only to witness a knock-out in the boxing-ring to observe a brain injury produced in front of their eyes without any damage to the skull bones. What is wanted is a new and descriptive word *for the laity to use* which implies brain injury without skull damage.—I am, etc.,

London, W.1. DESMOND FARLEY.

Dog-bite Wounds

SIR,—The article by Mr. M. L. H. Lee and Dr. A. J. Buhr (*Journal*, January 16, p. 169) is a welcome addition to the literature on *Pasteurella septica* infections of dog-bite wounds, and it was indeed gratifying that the authors observed a varying incidence corresponding with seasonal fluctuations noted by myself in the carrier rate in dogs.

The type of *Past. septica* occurring in the mouth, nose, and throat of dogs, and hence in dog-bites, is biochemically easily distinguishable from types found in other animals[1]; it also shows the properties of a bacterium in the rough or avirulent phase, and I believe this to be the reason why pasteurella infections rarely follow dog-bites yet are relatively common in bites inflicted by cats, which carry a more virulent type in their throats. Although the organism is very sensitive to hydrogen peroxide (10 μg./ml.)[2] strains from dog bites often have an unusually high catalase activity, suggesting that perhaps hydrogen peroxide solution, despite its short action, might be a rational cleansing agent for such wounds.

A study of *Past. septica* strains from a number of internal infections in humans (e.g., bronchiectasis) has led me to think that in such cases the source of the infection is usually cattle or pigs; two strains isolated from the throats of healthy veterinary students had similar properties,[3] and there is little doubt that the main factor here is contact with farm animals, meat, or offal, but not with household dogs.—I am, etc.,

Department of Pathology,
Royal Veterinary College,
London. J. E. SMITH.

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[1] Smith, J. E., *J. comp. Path.*, 1958, **68**, 315.
[2] Jordan, R. M. M., *Brit. J. exp. Path.*, 1952, **33**, 27.
[3] Smith, J. E., *J. comp. Path.*, 1959, **69**, 231.

Schultz–Dale Test for Carcinoma

SIR,—In reply to Dr. Jack G. Makari's letter in the *Journal* of November 28 (p. 1178), the controls that we used (*Journal*, October 3, p. 615) were those said to be satisfactory by Dr. Makari in the technique he described.[1] Our experiments were carried out to confirm the results that he obtained by this technique, and were discontinued when it became clear that such confirmation was not being obtained.

The calcium concentration of the Tyrode's solution employed by us was that used by Dale.[2] Lower concentrations were considered inadvisable, since Mongar and Schild[3] have shown that the release of histamine at this concentration is already reduced to nearly one-half of that observed with higher calcium concentrations. It is of interest that Dr. Makari has now stated that he uses a solution with ten times the usual magnesium concentration for Tyrode's solution, and that adjustment of the *p*H of the solution is called

for ; although in his original publication, on which the present work was based, air or oxygen–carbon-dioxide mixtures were said to be satisfactory alternatives for aeration. This would seem to have involved differences in the *p*H of his solutions.—I am, etc.,

L. M. MCEWEN.

Medical Research Council Department of Chemical Research, University College Hospital Medical School, London, W.C.1.

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1 Makari, J. G., and Huck, M. G., *Brit. med. J.*, 1955, **2**, 1291.
2 Dale, H. H., *J. Pharmacol.*, 1913, **4**, 167.
3 Mongar, J. L., and Schild, H. O., *J. Physiol.*, 1958, **140**, 272.

Alcohol and Road Accidents

SIR,—In the report by the special B.M.A. committee on alcohol and road accidents (*Journal*, January 23, p. 269) reference is made to the articles by Drew *et al.*[1] and by Cohen *et al.*,[2] and these articles are frequently mentioned in the general press. As these articles are referred to as having appeared in the *British Medical Journal*, anyone who has not seen the original articles may naturally assume that the authors are medically qualified. But, despite the fact that these articles appeared in the *B.M.J.*, none of the authors shows a medical qualification.

Devising a test equivalent to ordinary motoring is obviously extremely difficult, and, however ingenious an aptitude test may be, it does not necessarily even approximate to the truth. Drew's tests are said by the B.M.A. committee to be "reasonably realistic," yet his toy is unlike a real car in so far as the driver has no "feel" of the road surface or camber. What passenger would like to be driven by someone who, having had no alcohol at all, scores 209 kerb bumpings in a tracking test ? Cohen's drivers were expected to be able to judge the narrowest gap through which they could drive an 8-ft. (2.4-m.) bus, varying widths of gap being given, with a minimum of under 8 ft. This seems to imply the necessity to be able to drive to paint-scrape margins. The fact that Drew's and Cohen's drivers were progressively less efficient with graduated doses of alcohol only confirms already accepted works (e.g., *The Action of Alcohol on Man*, by Professor E. H. Starling[3]), but their experiments seem to ignore completely many of the innate relevant factors of ordinary motoring.

I believe that the conclusions of Cohen *et al.* and of Drew *et al.* should not have received the status of British medical opinion unless they were supported by colleagues with medical qualifications.—I am, etc.,

London, S.W.13. T. G. HOVENDEN.

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2 Cohen, J., Dearnaley, E. J., and Hansel, C. E. M., ibid., 1958, **1**, 1438.
3 Starling, E. H., *The Action of Alcohol on Man*, 1923. Longmans, Green and Co., London.

SIR,—I found your summary of the report of the special B.M.A. committee "Alcohol and Road Accidents" (*Journal*, January 23, p. 269) very interesting. There is no doubt that a concentration of alcohol in the body fluids above a certain level does impair the driving ability in a substantial proportion of persons, and also leads to impairment of judgment. But I believe there are other factors equally responsible for the appalling increase in the number of road casualties: (1) Under the present regulations a learner driver can learn to drive any motor vehicle, whatever its maximum speed, provided it is roadworthy, has L plates on it, and he is accompanied by a qualified driver. (2) Once a learner driver has passed his test there is nothing to stop him, provided he has the money, from buying a car capable of over 100 miles (161 km.) per hour. I think there should be some legislation preventing newly qualified drivers from driving high-speed cars for a certain period, say two or three years.—I am, etc.,

Liverpool, 18. H. J. PRATAP.

Modern Treatment of Alcoholism

SIR,—Your excellent and timely leading article on this subject (*Journal*, January 9, p. 117) stresses the fact that treatment of alcoholism is "a considerable responsibility on the medical profession." Doctors can only discharge this responsibility if they emotionally accept alcoholism as an illness and approach the alcoholic as a sick man in need of medical help, if they are well informed about the nature of alcoholism and about its early features, and if there are sufficient facilities available in which alcoholics can receive specialized out-patient and in-patient treatment.

Unfortunately all too often alcoholics feel, rightly or wrongly, that doctors do not really accept and welcome them as sick people who deserve skilled medical attention. Furthermore, the training of medical students does not prepare them to diagnose alcoholics in their early phases. In this country, as in the United States,[1] it is quite likely that for many years alcoholics maintain a more or less precarious foothold at home and at work and escape the well-known late physical and mental complications of "chronic alcoholism." Yet alcoholics often do not muster sufficient courage to ask for medical help early in their alcoholic career. If they consult doctors they often may do so for other complaints whilst playing down the extent of their drinking. Under these circumstances, as a rule, alcoholics are not diagnosed until they have reached the late stages.

Not only doctors but also the general public must have some knowledge and understanding of alcoholism to facilitate early diagnosis and successful rehabilitation. By taking an active interest in alcoholics doctors can give a lead to the general public and help in changing public attitudes towards the acceptance of alcoholism as an illness that could and should be treated. It is obvious that sobering-up is no more than the initial phase in the treatment of alcoholism. Often the rehabilitation programme requires the collaboration of several agencies and teamwork. It must be remembered that an alcoholic's treatment is incomplete without including his family in the therapeutic programme. No matter what the alcoholic's treatment in his acute phases, for the purposes of his long-term rehabilitation the help of Alcoholics Anonymous will be found invaluable. A.A. is only too anxious to provide doctors with information about groups and contacts in any part of the country.

As your leading article states, prognosis "depends to a decisive degree on the patient's incentive for cure. . . ." Under certain circumstances, however, it seems that motivation can be induced in some alcoholics who initially lack any notion of giving up drinking. It is therefore perhaps questionable whether it is right and in their best interest to stand by inactively and watch such people virtually committing suicide through compulsive drinking, ruining in the process also their families and endangering the emotional health of their children. Arguments that the old Inebriates Acts failed in the past,[2] just as apparently also similar recent attempts in Eire,[3] cannot be taken as a proof that treatment of the unwilling alcoholic is always useless: even

alcoholics willing to undergo treatment will very often be found "uncooperative" unless treated by an understanding and experienced staff under specialized conditions. It can be confidently expected that within a therapeutic community formed by alcoholics a certain proportion of at first reluctant patients will gradually change their attitude and achieve some measure of success.

Such therapeutic communities would be formed by the special regional alcoholic centres advocated in your article. The location of such centres should not be left to chance but should be well planned beforehand. Their further development should be adjusted not only "in accordance with the need" but also on the basis of findings and observations emerging from a well-planned research programme carried out alongside the therapeutic work. Problems of medical administration, clinical policy, and organization of such centres are discussed in detail in a pamphlet obtainable from the physician superintendent of Warlingham Park Hospital. Regional alcoholic units,[1] with their out-patient clinics and working in close collaboration with A.A., would also be ideal centres for professional teaching and public education and for research. The recovered alcoholic would become a more familiar figure and contribute his share in helping to dispel the widespread belief that alcoholics do not want to, and cannot, recover. In this way the stigma attached to a diagnosis of alcoholism will gradually be reduced and alcoholics encouraged to ask for help when still in the early phases of their illness.—I am, etc.,

St. Bernard's Hospital, Southall, Middlesex. M. M. GLATT.

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[2] *Alternatives to Short Terms of Imprisonment*, 1957. H.M.S.O., London.
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SIR,—Your leading article on the modern treatment of alcoholism (*Journal*, January 9, p. 117) was indeed welcome, as it shows that at last the medical profession are aware that alcoholism is in fact a disease. There is a lot that is still controversial and more that is unknown.

On prognosis you state: "Alcoholism may be a relapsing disease, but it carries a prognosis no worse than many (and better than some) other conditions that doctors treat." This can be clarified by the experience of workers in the U.S.A.,[1] where the expectation of life is estimated to be reduced from 10 to 15 years. Again, the experience of Alcoholics Anonymous indicates that this disease is truly progressive—ending with premature death, with or without preceding insanity, if not treated. I would challenge the figures of the College of General Practitioners survey.[2] How many practitioners in this survey can recognize the chronic addictive disease in all the three stages as defined by W.H.O.[3] ? I have spoken to one practitioner who took part in this survey and he appeared to recognize only the end stage or Stage III. Thus the figures and conditions of that survey are probably invalid, being underestimated.

Your suggestion of treatment centres on a regional basis is an excellent start. The results of work in this field in the U.S.A. have shown that quite a proportion of patients with this disease can be successfully treated as out-patients, after a set period in hospital for "drying-out." Dorothea F. Mindlin[4] has produced an excellent method of arriving at a prognostic index, which will assist with the initial screening of patients into in-patient and out-patient groups. When treatment centres are established, further research and an increase in knowledge will follow. It will also then become possible to estimate more accurately the incidence rate of this truly problem disease, which I believe is on the increase and may well increase rapidly in another 10 to 15 years when the effects of the high drinking habits of the present teenagers have their full impact.—I am, etc.,

Halifax. PETER M. SMITH-MOORHOUSE.

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Corticosteroids in Ophthalmology

SIR,—During the past few months I have had under my care three cases of moderately severe hypopyon ulcer of the cornea. These were treated, in the first place, by the usual orthodox methods including carbolization, atropine, and antibiotics by instillation, subconjunctival penicillin and streptomycin, artificial pyrexia, and sulphonamides by mouth. The first case did not respond to these methods, and, after some hesitation and rather in desperation, drops containing neomycin and hydrocortisone were instilled at frequent intervals. There was a dramatic improvement and clearing of the hypopyon followed by relapse when these drops were stopped. Further treatment with them resulted in cure of the hypopyon ulcer with a minimum of scarring.

In the other two cases orthodox methods were again tried, without a good response, and the same antibiotic and hydrocortisone drops were then given with the same prompt improvement and eventual cure. As antibiotic drops and subconjunctival injections had already been given without any marked improvement, I think it is reasonable to conclude that the addition of the hydrocortisone was a most vital factor in bringing about the immediate improvement, and I myself have no doubt that these hypopyon ulcers were cured largely because of, and not in spite of, the addition of hydrocortisone to the treatment. And why should not that be so ? Surely a substance which will reduce inflammatory oedema and exudation, and venous stasis, will have a beneficial effect by allowing the defences of the body and the antibiotics to get to the inflamed parts more easily.

These cases make me wonder whether Mr. J. Primrose (*Journal*, January 2, p. 60), who condemns so vigorously the use of these combinations of an antibiotic and hydrocortisone, has ever used them. He doesn't say that he has, and his entire condemnation is based on vague theoretical grounds. In that case, why should he refer so scathingly to these combinations of only two substances (with complementary actions) as blunderbuss therapy ? And, regarding his comparing their use to giving a mixture of atropine and eserine (with antagonistic actions), this seems to me a ridiculous analogy. The corticosteroids either alone or in combination with an antibiotic are not given because

a diagnosis is in doubt (as Mr. Primrose suggests) but because there isn't other treatment as effective. And, contrary to what you state in your annotation on this subject (*Journal*, November 21, p. 1079), in my experience the corticosteroids are most beneficial in some virus diseases of the eye—e.g., the keratitis and iritis of herpes zoster ophthalmicus—and in many cases of chronic corneal disease, if they don't cure, they often give most marked symptomatic relief, quite unobtainable by other means, which certainly the patients welcome.

Ophthalmologists are fortunate in being able to see what is happening to the inflamed eye and can regulate their treatment accordingly, and if by chance they think hydrocortisone is being harmful, or not helpful, they can stop it without dire consequences. In my opinion there is a tendency at the present time to exaggerate possible dangers in its local use in the eye.—I am, etc.,

Chester. A. C. SHUTTLEWORTH.

Pulseless Disease

SIR,—I read with great interest the article by Mr. J. M. Pahwa *et al.* (*Journal*, December 26, p. 1439) on the pulseless disease (Takayasu's disease). I should like to add the following points which are the results of our studies concerning Takayasu's disease.

It is known also as the Martorell–J. Fabré Tersol syndrome, after their full description of the condition.[1] Trophic changes affecting the tip of the nose, the lobule of the ear, and mucocutaneous junctions are very important and common clinical features of the disease. They are of insidious onset and result in indolent ulcerations.[2 3 4]

As regards the investigations in addition to aortography and angiocardiography, "pneumostratigraphie mediastinale," used by French investigators,[5] has been found very useful in directly demonstrating the vascular occlusion. Air is insufflated by the retrococcygeal route: this gives a clear picture of the mediastinum, and is very helpful in excluding other mediastinal conditions like tumours and aneurysms. E.E.G. is very useful in diagnosis. It usually shows a rapid rhythm of high voltage with depression at the occipital area.—I am, etc.,

St. Andrews Hospital,
Near Norwich. N. PAPANASTASSIOU.

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SIR,—In the article on pulseless disease or Takayashu's disease, Drs. J. M. Pahwa, M. P. N. Pandey, and D. P. Gupta (*Journal*, December 26, p. 1439) wrote, "The present paper records a further case, the first one from India." They have missed the two cases of pulseless disease already reported from India, one reported a long time before theirs. In an article entitled, "Case of Reverse Coarctation Syndrome, an Aortic Arch Syndrome,"[1] Sen Gupta and Ghosh described a man of 51 with an aortic arch syndrome characterized by absence of pulsation in all arteries of the upper limbs and neck, with high systolic blood pressure in the vigorously pulsatile arteries of the lower limbs, and evidence of collateral circulation on the abdominal and chest wall. The first case of aortic arch syndrome from India was reported by Shikhare.[2]—I am, etc.,

St. Tydfil's Hospital,
Merthyr Tydfil, Glamorgan. B. BANERJIE.

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Pulsating Umbilical Cord

SIR,—The writer of your annotation, "Pulsating Umbilical Cord" (*Journal*, January 9, p. 119), no doubt inadvertently, misrepresents the main point of an, as yet, unpublished paper by Dr. C. A. Smith and myself. I hope you will allow me to make a correction, so as to avoid possible confusion later. We observed that either asphyxia following delivery or apnoea developing later may cause a rise in an infant's blood pressure; but infants suffering from the respiratory distress syndrome described by Desmond and her colleagues,[1] to which your annotation refers, were noted to show a transient fall in blood-pressure.—I am, etc.,

Department of Child Health,
King's College,
University of Durham. G. A. NELIGAN.

REFERENCE

1 Desmond, M. M., Kay, J. L., and Megarity, A. L., *J. Pediat.*, 1959, **55**, 131.

Insulin Syringes

SIR,—In the *Journal* of January 16 (p. 204) Dr. B. Hirsh expresses concern over the confusion which exists among diabetic patients in the measurement of insulin. Those who treat diabetics will share his concern. This confusion arises, however, not, as Dr. Hirsh suggests, from the existence of 20-unit per ml. soluble insulin, but from the commonly used "insulin" syringe calibrated in 20-unit per ml. which is employed to measure 40- and 80-unit per ml. insulin. In fact many different types of syringes are used for insulin injection. Some are calibrated in 0.1 ml., some in 0.05 ml., others both in millilitres and minims. Syringes may be marked and numbered in units to measure 20-unit or 40-unit per ml. insulin. It is from the multiplicity of syringes used for this purpose that confusion arises. The introduction of the American model calibrated for both 40- and 80-unit per ml. insulin on the same syringe, as suggested by Dr. Hirsh, would, I think, add further to this confusion.

The problem of the insulin syringe can only be solved by the adoption of a standard type for use throughout the country. Such a syringe has been designed, with special consideration of the needs of the diabetic, by a British Standard Institution Committee, including representatives of the Ministry of Health, the British Diabetic Association, diabetic specialists, and syringe manufacturers. The syringe (B.S. 1619:1950) has been adopted by the Ministry of Health, who state, in the *Drug Tariff* issued for the guidance of retail pharmacists, that it should be generally supplied if an insulin syringe is prescribed on an E.C.10.

The B.S. 1619 is made in 1-ml. and 1.5-ml. sizes, and calibrated in 0.05 ml. (the 1 ml. being divided into 20 and the 1.5 ml. into 30 divisions). Reference to insulin units is deliberately omitted, and numbers on the syringe scale indicate the number of marks or divisions for ease of counting. When 20-unit, 40-unit, and 80-unit per ml. insulin is measured, each division represents 1, 2, or 4 units of insulin respectively. The divisions are wide and the marks clear for ease in

reading, particularly by patients with poor eyesight. All diabetics should be given an insulin dose-card with their insulin dose stated both in units and in marks on the syringe. This, with the B.S. 1619, can abolish all confusion. The B.S. 1619 has the additional advantage of a Luer mount to take Luer needles.

The 1-ml. model, measuring up to 80 units of insulin and meeting the need of most patients, has proved very satisfactory. The 1.5 ml., however, is clumsy to handle, and too long to fit a spirit-proof case. It is to be replaced by a 2-ml. syringe similar in type to the 1.0-ml. model. At the same time a spirit-proof case to take either syringe will be produced. Both syringe and case will, I understand, be available to the National Health Service patient. Their production is eagerly awaited by many, and the responsible authorities, aware as they are of the present unsatisfactory state of the insulin syringe, should see to it that it is no longer delayed.—I am, etc.,

St. Alfege's Hospital, London, S.E.10. B. A. YOUNG.

Barbiturate Deaths

SIR,—While one hesitates to enter into controversy with such an eminent authority on barbiturate deaths as Dr. S. Locket, nevertheless I feel that some points mentioned in his letter (*Journal*, December 12, p. 1332) must be commented upon. He appears to miss the point that the dosage of bemegride is quite ineffective while taken in such small quantities as are present in one or two of the combined capsules. It is only when the dose is increased to large quantities that the effect of the bemegride becomes active. This would appear to be borne out by his case where the patient was in light coma following the ingestion of a dozen or so of the combined capsules. It is reasonable to suppose that had this patient taken double that quantity he would have shown no harmful effects whatsoever.

Drs. E. M. Trautner, T. W. Murray, and C. H. Noack (*Journal*, December 28, 1957, p. 1514) lend further support to this argument, for they reported on the use of the combined drugs: "The absence of a primary coma may be assumed to be due to the antagonistic effect of the bemegride. As the dose of amylobarbitone was increased above 800–1,000 mg., we kept the patients under constant observation because it was feared that they might sink into a deep stupor or coma. This was never the case; on the contrary, *as the dose increased the sleep became lighter.*" (The italics are mine.) While it is obviously impossible to do a controlled study on the effect of these combined tablets in man, they do seem a possible answer to a very difficult problem, and every case reported—even my "series of one case"—must be of interest.—I am, etc.,

Newport, Mon. D. T. HEFFERNAN.

New Drugs for Depression

SIR,—We were interested to read the letter from Drs. F. A. Bleaden and Grazyna Czekanska (*Journal*, January 16, p. 200) reporting the alarming reactions they experienced in two cases out of four in which E.C.T. followed a short time after treatment with phenelzine.

In a controlled trial, soon to be reported, of some 150 cases using phenelzine ("nardil"), in dosage of up to 30 mg. three times a day, we have had cause to give E.C.T. to 21 patients (9 male, 12 female) mainly within one or two days of giving the drug. In four cases (2 male, 2 female) E.C.T. was given concurrently with phenelzine. All patients received modified E.C.T. using thiopentone and suxamethonium bromide ("brevedil E"). In this group of 21 patients we have not seen any evidence of the reactions reported by your correspondents.—We are, etc.,

I. FROST.
G. EGAN.
R. MIDDLEFELL.
H. EATON.

Deva Hospital, Chester, and the Liverpool Psychiatric Day Hospital.

SIR,—Drs. F. A. Bleaden and Grazyna Czekanska (*Journal*, January 16, p. 200) have reported two cases of collapse immediately following E.C.T. in four patients who were under treatment with phenelzine ("nardil"). In this unit of 60 beds in this hospital of 1,150 beds, over 200 treatments have been given in which E.C.T. has been combined with one of the antidepressant drugs, and, in particular, phenelzine, and no untoward reactions have occurred. Inquiries amongst my colleagues, psychiatric and anaesthetic, throughout this hospital reveal that they have had no experiences such as described by Drs. Bleaden and Czekanska. Far from phenelzine treatment being a contraindication to E.C.T., I find that combining E.C.T. with phenelzine is more effective than the use of either alone.—I am, etc.,

Tyrone and Fermanagh Hospital, Co. Tyrone. S. J. G. GILMOUR.

"Margot's Neuropathy"

SIR,—I would be glad of the hospitality of your columns to report an interesting and rather amusing little clinical observation.

We have a German nursemaid, and she told me that she had noticed "pins and needles" in her right big toe for about three weeks; this was present on rising in the morning and lasted the greater part of the day. In view of the possible significance of such a complaint arising suddenly in a young person, a clinical examination of the central and peripheral nervous system was undertaken. This, however, revealed no abnormality; the affected toe looked and felt all right, and it was difficult to assess any sensory impairment. The girl was otherwise healthy, and I decided to wait a couple of weeks and see what happened, before embarking on a full-scale hospital investigation. This was just as well, for in about a week the aetiology of the complaint was supplied by the patient herself.

It transpired that she was in the habit of sleeping with the sheets drawn tightly across the foot of the bed, very much in the way the hospital beds are made just before the chief's ward round. This had succeeded in maintaining the great toe of the uppermost—i.e., right—foot in acute flexion for most of the night, and her symptom can be explained as follows. Prolonged immobility of the toe in the flexed position brought about the following changes: (1) Venous stasis and local hypoxaemia, producing impaired nerve conduction. (2) Local oedema, by pressure on the adjacent nerve and its nutrient blood vessels, can cause a neuropathy, as mentioned by Dr. J. E. Forster (*Journal*, September 5, p. 369) when discussing the aetiology of the carpal tunnel syndrome, and I feel that in this case also these factors were operative. (3) Simple mechanical traction on the nerve will bring about altered function.

In honour of our nanny, I have called this condition Margot's Neuropathy, and I am eagerly awaiting the day (and the assured kudos) when I can diagnose it in a "real" patient. The treatment of this condition, unlike many nerve disorders, is very simple, and relatively inexpensive.—I am, etc.,

Ashton-in-Makerfield, Lancs. N. TREVOR BURNETT.

Giant Salivary Calculus

SIR,—Dr. S. S. Ahmed says (*Journal*, December 12, p. 1335) that stone in the submandibular duct is a common condition. I think that European surgeons do not agree with him. In fact, this affection—like lithiasis generally—is much more common among Arabs than among Europeans. In 1958, when I was assistant surgeon at the government hospital of Benghazi, I saw many cases of calculi of the salivary ducts. One of these was remarkable because of the size of the stone; it measured 6 × 4 cm., its form was oval, and its colour yellow. The patient, a male aged about 40, had had it for two years, without serious trouble except slight pain. The extraction of the stone from the submandibular duct, as in the case reported by Dr. Ahmed, was very easy, a Spencer Wells forceps used as lever being sufficient.

I think that the reasons why lithiasis is so common among Arabs should be investigated.—I am, etc.,

S. Stefano d'Avelo, Italy. EUGENIO BEER.

Space Travel

SIR,—I read the leading article entitled "Keeping the Planets Clean" in the *Journal* of October 24 (p. 811), and expected to find some comments in your correspondence columns, but up to the present I have not seen any.

Attempts to sterilize a space vehicle deserve to be commended even if they are only partially successful, but to sterilize it for the return journey is even more important, and it is not clear how this is to be done. Space travellers on their return to the earth from other planets, if they ever do return, may bring with them bacteria and viruses to which human beings possess no natural immunity. These may give rise to world-wide epidemics, resulting in the deaths of millions of people.

So far as I am aware the medical profession and the Ministry of Health in the United Kingdom—to say nothing of other countries—have made no preparations to deal with such a contingency. It would therefore be prudent to discourage all projects for space travel until a tentative scheme has been evolved to cope with consequences of a dangerous nature.—I am, etc.,

George, Cape Province, South Africa. A. J. C. TINGEY.

Smokers' Lung Cancer

SIR,—The heavy cigarette-smoker almost invariably has a chronic cough. It is possible, if not probable, that smokers' lung cancer is due primarily to this cough and only secondarily to the carcinogens in the smoke. It is also probable that the chronic cough is due to some irritant in the smoke from cigarette-paper and not from the tobacco-smoke.

Why do heavy cigarette-smokers almost invariably develop a cough, whilst heavy pipe- and cigar-smokers seldom or never do? At first sight, the answer to this question appears obvious. Smoke from the pipe is cooled as it passes through the stem, and a large proportion of the carcinogens are deposited in the pipe-stem, whilst cigarette-smoke is neither cooled nor condensed but is inhaled unchanged.

The writer has not had the opportunity to carry out any extensive investigation, but he and a few of his patients found that, whereas their chronic cigarette-cough cleared up fairly rapidly after a few weeks' abstinence from cigarettes and in place thereof fairly heavy pipe-smoking, on the other hand the coughs were not abated at all by many weeks of smoking cigarettes from holders with stems as long as the pipe-stems. Quite clearly the mere passage of the smoke through the stem did not rid it of the power to maintain the cough. It was also found that smoking cigarette-tobacco from a pipe did not cause a cough to develop, whereas the same tobacco rolled into cigarettes did. Nevertheless, there is very definite evidence that heavy smokers are more prone than light smokers and non-smokers to develop lung cancer. The evidence in question also indicates that it is the heavy cigarette-smoker who, above all other tobacco-smokers, exhibits this proneness. If smokers' lung cancer is due solely to the carcinogens in tobacco-smoke, why are heavy pipe- and cigar-smokers practically immune?

Recent contributions on the association of lung cancer and chronic pulmonary disease are of particular interest in this connexion. Fink,[1] concluding his review of chronic pulmonary disease in patients with lung cancer, states that 65% of one group had long-standing bronchitis. Reid and Fairbairn,[2] in their follow-up study of men with chronic bronchitis, reported that in a group investigated over a seven-year period the number of deaths from lung cancer was four times as many as expected. Higgins,[3] writing of tobacco-smoking, respiratory symptoms, and ventilatory capacity, stated that a clear relation between smoking and persistent cough and sputum has invariably been found, and smokers also tended to record more chest illnesses than non-smokers. He also states that, though pipe-smoking did not appear to be entirely harmless, it did seem to be much less apt than cigarette-smoking to cause symptoms of chest complaints. There is a definite implication in Higgins's communication that he believed chronic cough was more important than carcinogens.

In these simple little experiments it was found that only when paper-smoke was added to tobacco-smoke did a cough develop, and it is, at least, not unreasonable to suggest that the cigarette-smoker's cough is due to some irritant in the paper-smoke and not to tobacco-smoke. In conclusion it is suggested that it would be well worth while trying to identify the irritating component in cigarette-paper smoke. If it can be identified, the manufacturers of the papers should be able to eliminate it and make cigarettes as innocuous as cigars.—I am, etc.,

Queensland, Australia. H. LEIGHTON KESTEVEN.

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"Do-it-Yourself" Enuresis Alarm

SIR,—Having an adult enuretic in my practice, I was interested in the ingenious "Do-it-Yourself" enuresis alarm described by Dr. J. B. Metcalfe (*Journal*, December 26, p. 1488). As I had no monel metal gauze I used some of the aluminium foil in which my wife was cooking the turkey. This is available in 12 in. × 20 in. (30 cm. × 50 cm.) rolls for 2s. 11d. The upper mat was perforated by interleaving it with newspaper, folding it round a ruler and cutting V-shaped pieces from the resulting roll. Ordinary paper-clips, soldered to the wires, were used as connectors to the foil, which was folded over a piece of card where the connexions were made. Testing was by touching the two paper-clips together. The cost of the apparatus was 13s. 8d., including enough foil for nine mats. The alarm works well, and the patient and I are most grateful to Dr. Metcalfe.—I am, etc.,

Drayton, Norfolk. JOHN GALE.

Conjoined Twins

SIR,—Referring to the letter by Dr. Xto G. Okojie about conjoined twins (*Journal*, January 9, p. 129) I append a photograph of a set of twins delivered at the Iraqi College of Medicine Teaching Hospital, Bagdad. The twins, both females, can be classified as craniopagus, with fusion occurring in the lower part of the face and in the thorax, so that the mouth is represented by a single long slit, and the two adjacent eyes are very close together and partly fused. There is partial fusion

down to the level of the umbilicus, which is single, though there are four upper limbs. Below the umbilicus the twins are entirely separate. The foetuses presented by the four feet and were dead before birth. Delivery had to be completed by doing craniotomy.

It is strange, in view of the rarity of the condition, that I should deliver these twins only two months after the delivery of another and rather more completely fused set (complete fusion below the umbilicus), which was being studied at the anatomy department of the College.—I am, etc.,

Edinburgh, 12. K. KUBBA.

Massive Gastric Haemorrhage after Salicylate

SIR,—In your excellent leading article on "Aspirin Plain and Buffered" (*Journal*, February 7, 1959, p. 349) you mentioned that aspirin can produce erosive gastritis with haemorrhage. Recently a patient was admitted to the Royal London Homoeopathic Hospital with massive haematemesis and melaena after taking "disprin" (acetylsalicylic acid and calcium carbonate). Salicylates reduce the plasma prothrombin, which in all probability increases the tendency for gastric erosions to bleed profusely.

A man aged 35, non-alcoholic, non-smoker, without any past history of dyspepsia, bleeding, or other serious illness, had been taking six tablets of disprin per day for headache. On the fourth day he felt sick, vomited a pint (0.6 litres) of blood, passed a large melaena stool, and collapsed. He was rushed to hospital. He was shocked and sweaty, with a rapid pulse of low tension (140/minute): B.P. 95/60; temperature 97° F. (36.1° C.); Hb 62%; abdomen, soft with normal bowel sounds. Routine anti-shock measures were instituted—i.e., morphine, blood transfusion, and so on. A stomach tube was passed; pulse and blood-pressure readings were frequently recorded.

In spite of adequate resuscitation measures and the transfusion of six pints (3.4 litres) of blood, his condition remained critical and caused anxiety. It would have been reasonable to assume that he had developed irreversible oligaemic shock, but fortunately it was not so. We decided to operate. At laparotomy all the abdominal organs including the liver were found normal. There was no visible or palpable ulcer in the stomach or duodenum, but the stomach was grossly distended. On opening the stomach a mass of blood clot was found, the removal of which led to steady improvement of his pulse and blood-pressure. It was apparent that in addition to blood loss distension of the stomach was in part responsible for the state of shock. A search inside the stomach failed to reveal any ulcer or bleeding point. A partial gastrectomy was therefore carried out in the hope that adequate resection would remove the undiscovered source of bleeding.

The patient stood the operation well. When he left the operating theatre his B.P. and general condition had improved considerably. Examination of the resected portion of the stomach revealed to our surprise that a small bristle-like end of a vessel had been the source of the massive bleeding. That such massive bleeding can come from a small vessel has been stressed by Tanner and Avery Jones.[1] Post-operatively the patient had no gastric symptoms and he has since been discharged to convalesce.

—I am, etc.,

London, W.C.1. M. A. HOSSAIN.

REFERENCE

[1] Tanner, N., and Avery Jones, F., *Modern Trends in Gastroenterology*, 1958, 2nd series. Butterworth, London.

Peptic Ulcer in Africans

SIR,—Your annotation on "Peptic Ulcer in Africans" (*Journal*, June 6, 1959, p. 1462) has evoked much interest among clinicians working in tropical Africa, and I agree with Dr. S. V. Humphries (*Journal*, December 5, p. 1253) that the incidence of peptic ulcer seems to vary in different parts of the continent. Dr. Humphries states that as a mine medical officer in Sierra Leone he did not see a single case of clinically recognizable peptic ulcer, but from my experience the condition is not quite as rare in that area as might be implied from his remarks.

While stationed in Freetown from November, 1955, to August, 1959 (less six months' leave), I had 86 Africans referred to me for barium studies on account of dyspepsia, with the following results:

	Males	Females	Total
Duodenal ulcer (proved) ..	22	1	23
,, ,, (suspected but no definite ulcer demonstrated) ..	9	1	10
Gastric ulcer (high up on lesser curvature)	6	—	6
Gastric ulcer (prepyloric) ..	2	—	2
Anastomotic ulcer	1	1	2
Carcinoma of stomach	6	—	6
No abnormality discovered ..	30	7	37

Most of these patients were living in or around Freetown, which has a population of approximately 100,000 persons, and only a few (about a dozen) were sent in from the Protectorate. The difficulties in assessing the true incidence of peptic ulcer in Africa have been described by Drs. A. G. Shaper and A. W. Williams (*Journal*, October 17, p. 757), who also remarked that although some of the patients in their series were well educated or relatively well-to-do, the majority were of a much lower social status.

Of the 33 patients in my series who had proved or suspected duodenal ulcers, 13 had received some form of higher education and held responsible appointments or were students working for academic qualifications. As people of this status had reasonably easy access to me, I think it is likely that this figure is not far from giving a true indication of the incidence of peptic ulcer among the more highly educated and well-to-do members of African society in Freetown, who, according to my estimate, would not number more than 500–1,000, including students. The

remaining 20 with proved or suspected duodenal ulcers and all 8 cases of gastric ulcer and 6 with carcinoma of the stomach came from the lower socio-economic groups. As already mentioned, it is extremely difficult to assess the true incidence of peptic ulcer among the general population. As, however, I was the only person in Sierra Leone having charge of an *x*-ray machine capable of barium studies, I think it is reasonable to suppose that I would have had more than the mere handful of patients that were referred to me from the Protectorate if peptic ulcers were common there. This is in agreement with Dr. Humphries's experience. It is my opinion that the incidence of duodenal ulcer is very much lower among the general population than among those holding posts of responsibility. "Stress" was an obvious factor in the latter group, and several volunteered the information that their symptoms were exacerbated during periods of overwork and mental strain.

It may well be that as Africans take over the burdens and responsibilities of administration and management in business and politics, so the frequency of peptic ulcer will rise in this group, while it will remain a comparative rarity in the non-civilized areas where the African continues to live his happy-go-lucky, day-to-day existence, letting to-morrow take care for itself.—I am, etc.,

Queen Elizabeth Hospital, Khormaksar, Aden. F. STEPHEN CARTER.

Reading the Number Plate

SIR,—Dr. R. A. D. Crawford's letter in the *Journal* of January 30 (p. 352) prompted me to take a look at my Colony of Singapore driving licence issued in 1948, which carried my bespectacled photograph and an endorsement that "Holder must wear eye glasses when driving."—I am, etc.,

Fleet, Hants. J. COUTTS MILNE.

Treatment of Pilonidal Sinus

SIR,—May I offer my sincere apologies to Mr. Robin Burkitt (*Journal*, September 26, 1959 (p. 579), and December 19 (p. 1406)) and to A. W. Anderson (*Boston med. surg. J.*, 1847, **36**, 74) for having wrongfully accused them of practising or expressing the intention to practise the operation of marsupialization? I should have written "simple unroofing," including in this term the practice of "laying open the tracks" (Mr. Burkitt's expression) with that of "exteriorization of the sinus track and its ramifications," the phrase used by Mr. P. G. Collins (*Journal*, September 12, p. 430), whose contribution Mr. Burkitt commended. May I also take this opportunity to draw attention to the misprint in the published version of my own letter (*Journal*, December 5, p. 1256)? In the second paragraph at the 13th line, in place of the words printed "lesions; grafting is for very large ones and recurrences." the following ought to have appeared: "primary closure should be avoided after excising recurrences."—I am, etc.,

Clinica Chirurgica, Padova, Italy. ROGER BREARLEY.

*** We apologize for the printing error.—ED., *B.M.J.*

Werner's Syndrome

SIR,—The paper on "Werner's Syndrome (Progeria of the Adult)" (*Journal*, November 7, p. 920) contains the statement, "The only previous post-mortem report is that of Oppenheimer and Kugel (1941)." I should therefore like to direct your attention to a paper by Perloff and Phelps,[1] of the Department of Medicine, Georgetown University Medical Center, Washington, D.C., entitled "A Review of Werner's Syndrome, with a Report of the Second Autopsied Case." In this paper the authors suggest that the abnormalities found in Werner's syndrome may be genetically determined. The authors of the report in the *Journal* should, however, be accorded recognition for their specific suggestion of a generalized tissue-enzyme defect causing premature senescence as the aetiological basis for the disease.—I am, etc.,

Seaside Memorial Hospital, Long Beach, California. GEORGE X. TRIMBLE.

REFERENCE

[1] Perloff, J. K., and Phelps, E. T., *Ann. intern. Med.*, 1958, **48**, 1205.

The Blind Beggar

SIR,—There is another, and much older, memorial to Henry de Mountfort a short distance from Miss Frink's statue in Bethnal Green (*Journal*, January 23, p. 289). This is a well-known public-house—"The Blind Beggar"—which stands next to Mann Crossman's brewery in Whitechapel Road. I do not know whether it was by chance or by design, but for some years prior to 1952 an old blind man stood outside selling matches. After the great fog of that year, he was never seen again.—I am, etc.,

J. P. J. ENTRACT, Librarian, The London Hospital Medical College.

London, E.1.

POINTS FROM LETTERS

Hypnosis by Laymen

Dr. A. A. MASON (24, Avenue Road, Regent's Park, London, N.W.8) writes: As the secretary of the British National Division of the International Society for Clinical and Experimental Hypnosis, I have been approached in the last week by Dr. Ainslie Meares, who is the Australian president of the same Society, and Dr. H. Grant-Whyte, who is a member of the South African Medical and Dental Council. Both these doctors are investigating the problem of lay hypnotists and the possible harmful effects which can be caused by the use of hypnosis by unqualified practitioners. Dr. Grant-Whyte has approached the Minister of Health in an attempt to get legislation in South Africa along the lines of the British Hypnotism Act, 1952, and also in an attempt to restrict the practice of unregistered and untrained persons. . . . I would be grateful, therefore, if any doctors who have evidence from their own practice of patients suffering harm following the use of hypnotism by unqualified practitioners could communicate the details of such cases to me.

Cross-infection in Hospital

Dr. PETER J. C. WALKER (Wall Heath, Staffs) writes: With reference to Dr. W. E. Crosbie's letter (*Journal*, December 12, p. 1331) concerning cross-infection in hospitals and hospital cleanliness, the cleanliness of hospitals should be a concern of all who occupy and work in them. However, there seems to be need for co-ordination and continued supervision and maintenance of such cleanliness—which must be acceptable and *proved* by medical people for medical people. The medical staff of all hospitals must go about their daily tasks free from the bogy of cross-infection. I tender therefore that, as this problem is now approaching a serious magnitude, "specialist" consultation and supervision is highly desirable. . . . I further suggest that the person who has the experience in co-ordination and the medical training necessary for such a specialist post (and also the time needed) is the district medical officer of health.

Obituary

S. R. SINCLAIR, M.B., B.Sc., F.R.C.S.Ed., D.O.M.S.

Mr. S. R. Sinclair, consultant in ophthalmology to the Royal Victoria and Belfast Ophthalmic Hospitals, died suddenly in London on January 18. He was 47 years of age.

Samuel Ronald Sinclair was born in Belfast on May 17, 1912, and was educated at Royal Belfast Academical Institution and Campbell College, where he played rugby football and cricket for the school. At Queen's University, Belfast, he graduated B.Sc. in 1932, and M.B., B.Ch., B.A.O. in 1936. He then became resident medical officer in the Royal Victoria Hospital, and during his time there became interested in ophthalmology, and subsequently became ophthalmic house-surgeon at St. Thomas' Hospital, London, in 1937, and clinical assistant at the Royal London Ophthalmic Hospital in 1938. Later he became registrar at the Belfast Ophthalmic Hospital. At the outbreak of the first world war he was commissioned in the R.A.M.C. and served in France and the Middle East as ophthalmic specialist with the rank of major.

On his return he joined the staffs of the Royal Victoria Hospital and the Ophthalmic Hospital, Belfast. Admitted a Fellow of the Royal College of Surgeons of Edinburgh in 1947, he took the D.O.M.S.(Eng.) in 1949, and then was appointed ophthalmic consultant to both these hospitals, posts which he held at the time of his death. He later served in the same capacity at the Belfast City Hospital, Downe Hospital, and Daisy Hill Hospital at Newry, and also at Omagh for a period. He was honorary secretary of the medical staff committee of the Royal Victoria Hospital, a member of the Belfast hospital management committee, and of the hospital committee of the Royal Victoria Hospital. In all these offices he served with great efficiency.

An expert golfer, he was a member of the Queen's University golf team in 1934–5–6, being captain in 1936, and in this year also was in the winning pair of the Irish Golf Championship mixed foursomes. More recently he became a keen yachtsman, and he and his family enjoyed week-ends at their house on Strangford Lough, where he also obtained much pleasure from bird-watching. He was also an enthusiastic racegoer, and enjoyed good music.

Mr. Sinclair married Joyce, daughter of C. G. Dickson, a former High Sheriff of the City of London, and they had three daughters, who are still quite young. His chief interest was his family, and he was a devoted husband and father.

F. A. M. writes: The sudden passing of Sam Sinclair came as a great shock to his friends and colleagues, since he was seldom ill and showed no warning signs. Being of such genial and friendly personality, he will be greatly missed by a wide circle, and in fact by all those with whom he came in contact in his work and recreation. He was a most expert operator, always calm, decisive, and efficient, and his judgment and diagnostic skill were of a high order. His opinion was often sought by his colleagues.

As a colleague he was ideal; those who knew him well can say that they never saw him ruffled, and in medical or administrative matters his opinions were always considered, balanced, sound, and helpful. He was an excellent companion at any time, especially for his qualities of friendliness and consideration for others, and this was particularly noticeable in his own home, where he was the perfect host, generous and courteous at all times. His patients adored him for his kindly and dignified sympathy extended to them impartially in consulting-room or hospital. For them his place will be very difficult to fill.

To his mother, wife, and three daughters we all extend our very sincere sympathy on the loss of such a son, husband, and father.

A. H. D. SMITH, *M.C.*, M.B., Ch.B.

Dr. A. H. D. Smith, who was formerly in practice in Llanelly and a notable figure in the public life of Carmarthenshire, died on January 31 at a Chepstow hospital. He was 69. For a number of years past his activities had been curtailed by illness.

Alexander Hugh Dickson Smith was born on May 21, 1890, at Llanelly, where his father, a Scot, was a head-teacher. Educated at Llandovey College and the University of Edinburgh, he graduated M.B., Ch.B. in 1914. After a short time at the Rotunda at Dublin he joined the R.A.M.C. and was sent to France, where he was attached to the Guards Division. Awarded the *M.C.* in 1917, he also received a certificate of merit from the G.O.C. Passchendaele. Later he served with the 3rd and 29th Divisions and finished his war service in India.

On his return to his native town of Llanelly in 1919 he at once entered upon general practice with Dr. John Davies and soon created for himself a very high reputation. Early on he became attached as surgeon to the Llanelly and District Hospital and for many years was actively engaged in surgery. In addition, he found time to master the elements of radiology and was appointed the first radiologist to his hospital. He filled the posts of surgeon and radiologist as well as satisfying the demands of an active general practice until the outbreak of the second world war.

During these years Dr. Smith played a most active part in the medical and Territorial life of his town and district. He was medical officer to the fourth battalion of the Welch Regiment and was closely concerned with its activities.

In 1935–6 the so-called "Llanelly dispute" took place between the doctors of the town and district and the trade unions. After having been honorary secretary of the South-West Wales Division of the B.M.A. Dr. Smith was elected chairman of the Division in 1936, and he was also chairman of the Llanelly and District Medical Society at the time of the dispute. Dr. Smith and Dr. Oscar Williams negotiated the settlement at Transport House, with Dr. Charles Hill and Dr. Guy Dain from Headquarters, and it was in large measure due to Dr. Smith's ability as a negotiator and organizer that this dispute finally resulted in a settlement satisfactory to all parties.

In 1939 Dr. Smith was called to the colours and went to France with the rank of Lieutenant-Colonel as O.C. of a surgical division of the B.E.F. In 1940 he returned to Britain and thereafter served as O.C. of various establishments in the Western Command. He was High Sheriff of Carmarthenshire for 1944–5 and in 1952 was appointed Deputy Lieutenant of the county. From this time on Dr. Smith's health started to fail. He gave up his general practice but continued to work actively on various statutory bodies, remaining for a time chairman of the Carmarthenshire executive council, of the Ministry of Pension boards for Swansea and Carmarthen, of the Advisory Committee for Disabled Persons under the Ministry of Pensions, and of many other committees. For many years he was a medical referee to the Ministry of Pensions. Dr. Smith during his years of active life did much for the B.M.A. and was president of the South Wales and Monmouthshire Branch from 1945 to 1946.

The interests of ex-Service men were very close to his heart; he was president of the Carmarthenshire branch of the British Legion and also of the Llanelly and District branch of the "Old Contemptibles" Association; his last

appearance in public was with this latter organization. He always remained keenly interested in Llandovery College, and for many years he had been a trustee and member of the board of governors. While at Llandovery he played cricket for the school, and throughout his life, in spite of the fact that his many activities precluded him from actually playing, he maintained a keen interest in the game. His election to the M.C.C., even though coming after the breakdown of his health, was a source of great satisfaction to him.

With the death of Dr. Smith, Wales, and Britain as a whole, has lost a medical practitioner of a type which it seems unlikely that under the present conditions of medical practice we can ever again see in this country. The medical profession has lost a great leader and organizer whose impress still remains on the present state of the practice of medicine in his own district. But it is as the general practitioner, full of understanding and never lacking in care and attention for his patients, that his name will live longest in the memories of his fellow townsmen and women.

He leaves a widow, Joan Margaret, daughter of the late Dr. Hugh John, of Llangennech, Carmarthenshire, and a daughter.—S. C. D.

O. W. writes: Dr. Smith suffered considerably during the last years of his life. His patients, fellow medical men, and many friends will long remember his general and surgical skill, his great devotion to all his patients, and his loyalty to the B.M.A. and to his colleagues.

O. C. M. DAVIS, M.D., D.Sc., LL.M., M.R.C.P. F.R.I.C.

Dr. O. C. M. Davis, honorary consulting physician to the Bristol Royal Hospital for Sick Children and Women and formerly head of the department of forensic medicine at Bristol University, died on January 24 at the age of 82.

We are indebted to Professor C. BRUCE PERRY for the following appreciation: For forty years O. C. M. Davis was a member of the staff first of University College and later of the University of Bristol. Few can have served an institution so loyally for so long or in such varied capacities. His main appointment, which he held for 39 years, was in the department of chemistry, where he taught generations of medical students and to whom he was always known affectionately as "O. C. M." While still teaching chemistry he graduated M.B., Ch.B. in 1916 and subsequently proceeded to the M.D. and took the M.R.C.P. In 1919 he was appointed physician to the Bristol Royal Hospital for Sick Children and Women, where he served faithfully till 1936, when he resigned. Although working as a physician and also developing an increasing interest in the law, he continued to work in the chemistry department and was appointed reader in medical chemistry in 1932.

O. C. M. Davis must have been invaluable to a young and growing medical school because he was always willing to help with teaching in almost any department. When it was decided that dental students should be taught the rudiments of medicine he became the first lecturer in medicine to dental students. In 1926 he was appointed head of the department of forensic medicine, and from then on he gradually became more and more interested in the study of the law, and, despite his many and heavy teaching duties, he succeeded in qualifying as a barrister. In addition to all the other responsibilities which he undertook he assisted with the teaching of materia medica and therapeutics from 1905 to 1941, and even after his official "retirement" in the latter year he agreed to continue for another year to help with the teaching of pharmacology. After his retirement from the university he much enjoyed practising as a barrister and contributed papers to law journals on medico-legal problems.

As can be seen from this career, he was always keenly interested in medical students and their work, and his tall, slender, upright, and austere figure and his rather sarcastic, yet never really unkind, tongue will still be vividly remembered by doctors and dentists all over the world who qualified in Bristol during the first forty years of this century.

R. B. MILNE, M.B., Ch.B.

Dr. R. B. Milne, who practised for many years in Reading, died suddenly at his home there on January 17. He was 61 years of age.

Robert Bruce Milne was born in Ballater, Aberdeenshire, on April 24, 1898, and was educated at Robert Gordon's College, Aberdeen, and Aberdeen University, where he graduated M.B., Ch.B. in 1922. During the first world war he was commissioned in the 4th Gordon Highlanders in Mesopotamia and India. A keen sportsman and athlete, he was a double blue (athletics and Rugby) at his university, and he was president of Aberdeen University Students' Union. After qualification he held hospital appointments, including that of senior house-surgeon, at the Borough Hospital, Bootle, and had some experience of general practice in West London. He went to Reading in 1924 as partner to Dr. Franklin Cox and Dr. Saunders Jones, and continued in very active general practice until the time of his death.

W. G. T. writes: One of Dr. Milne's chief interests was the welfare of his chosen profession, and for many years his scanty leisure hours were devoted unselfishly to the committee work which is now inseparable from the organization of medicine. He was a member of the Reading local panel committee from 1927 until the inception of the National Health Service, when his enthusiasm and drive were fittingly recognized by his appointment as chairman of the local medical committee and vice-chairman of the Reading executive council and chairman of its ophthalmic service committee. When he resigned, owing to ill-health, from these appointments in 1954, the doctors of the town made a handsome presentation to him, and the executive council's resolution recording appreciation of his "fine example in public service" was inscribed on vellum and presented to him at a ceremony in his honour. A member of the executive committee of the Queen Victoria Institute for District Nursing since 1929, he was a trustee at the time of his death.

Under his guidance, and that of others in similar positions in the other branches of the Health Service in Reading, mutual co-operation reached a level which must have been equalled only in very few other boroughs in the country. Facilities such as open access to *x*-ray and pathological departments and general-practitioner maternity beds, which are now an accepted part of the life of the Reading family doctors, were the result of negotiations in which he played an extremely active part.

The old type of family doctor is fast disappearing. Dr. Milne was one of a rapidly diminishing élite. To his patients he was essentially a family doctor who took a deep personal interest in their welfare, and to whom nothing was too much trouble if it would be of help. He was painstaking and careful to a degree, and his consulting hours went on for many hours past their advertised time. He lived for his work and drove himself unceasingly. To his fellow doctors he was an enthusiastic, scrupulously ethical and honest, and loyal colleague, a staunch member of the B.M.A. and the local executive, and an ardent exponent of the status of the family doctor. To the town of his adoption he was a prominent member of the community, synonymous with all that was best in the medical profession. To me, he was a respected chairman, a close personal friend, and a warm and sympathetic personality.

The doctors and citizens of Reading have lost one of their most respected and active colleagues. All were deeply grieved by his sudden and unexpected death at the height of his full life. He is survived by his devoted widow and four sons, one of whom has followed him into the medical profession. To them and his partners go the deep sympathy of his friends and colleagues.

Medical Notes in Parliament

REPORT ON REMUNERATION NEXT WEEK

The report of the Royal Commission on Doctors' and Dentists' Remuneration is to be published on February 18. The date was announced by the MINISTER OF HEALTH in answer to a question by Mr. M. MCLAREN (Bristol, North-west, Con.) on February 5.

DRUGS FOR PRIVATE PATIENTS

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Parties Demonstrating Their Strength

The Conservative back-benchers' motion urging that drugs and medicines should be made available for private patients has attracted support from about 100 members of the party. It has also drawn an amendment in the contrary sense from the Labour side, which made its appearance on February 4 with more than 60 signatories.

The practice of drafting motions in this way, having them printed on the Order Paper, and canvassing adherents to the opinion they express, may be regarded as in the nature of a reconnaissance in force. It has the dual purpose of ascertaining the extent of the support that the particular issue is likely to command, and by demonstrating this to the party leaders—for the operation is by no means mounted solely against the Government of the day—seeking to influence the direction of policy. Such motions rarely come to a debate in the House. Many are no more than passing demonstrations by small groups. The others either wilt from lack of encouragement, disappear after a definite assertion of official disfavour, or succeed to a greater or lesser extent in achieving their purpose by the pressure they can exert.

Motion and Amendment

In the present case the Conservative motion was initiated by Mr. A. MARLOWE, Q.C. (Hove, Con.), last December, and at first had four names attached to it. Its appearance followed the questioning of the Minister of Health in November which produced his demand for evidence of the detrimental effect on private practice which was being complained of.*

This motion asked the House to declare that

"noting that the number of doctors in private practice is rapidly diminishing, [it] is of opinion that the patients of such doctors should be enabled to obtain their medicines and drugs and have their prescriptions made up on the same terms as apply to National Health Service patients; and urges the Government to introduce the necessary legislation to achieve this."

On matters of substance the counter-move follows the same course. An amendment to the motion is drafted and tabled, and adherents invited. In this instance the initiative was taken by Mr. L. PAVITT (Willesden, West, Lab.), who until he relinquished the duties on being elected last October was national organizer for the Medical Practitioners' Union. He and his friends would substitute a motion which

"congratulates the medical profession on the efficient manner in which it has fulfilled its obligations under the terms of the National Health Service; deplores the attempt to remove any effective control over Government expenditure on drugs by providing them free to private patients; and urges the Government to resist pressure to introduce legislation which may lead to two classes of patients within the National Health Service."

Time for Debate

Additional force can be placed behind demonstrations of this kind by a further move. Mr. MARLOWE used this on February 4, when in the weekly interrogation of Mr. R. A. Butler, Leader of the House, about future business, he asked when time would be given to debate the motion. He claimed that it conformed to what had been Conservative policy since 1949, it was time that it was discussed, and "if it is not ventilated some of us may become a little restive." Mr. BUTLER turned aside the last observation—"I find it hard to recognize Mr. Marlowe under that description"—agreed it was an important matter, said he could not at present offer any time for debate, and suggested that Mr. Marlowe might discuss the matter with him.

*See *British Medical Journal*, December 5, p. 1265.

BILLS IN PROGRESS

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Laboratory Service for Industry

Lord TAYLOR ranged widely over the growth and activities of the laboratory service when the Public Health Laboratory Service Bill was discussed in the Lords on second reading on February 4, and found much to praise. The service had put Britain in the forefront of bacteriology and epidemiology; he wanted to see it develop; and he entered an immediate claim for the industrial health service to be one of the beneficiaries of that development. It needed a national laboratory service to do for workers in industry what the service was doing for doctors in public health, hospitals, and general practice. The service could do that with a minimum of alteration and a minimum of cost, and without the necessity for setting up a new organization. He also had some criticisms to offer of the proposed constitution of the administrative board. All these points had been left for consultation between Ministers before being examined again on the committee stage.

Clash on "Mutational Births"

The Population (Statistics) Bill has reached the Commons from the Lords and began its course there on February 1. Dr. EDITH SUMMERSKILL (Warrington, Lab.) saw in the information that it was proposed to collect about stillbirths some relation to the genetic effects of nuclear radiation, and made a severe attack on Ministers for having sought to evade making this clear. It had been said that the medical and midwifery associations were in agreement with the Bill. But, Dr. Summerskill said, they welcomed it because they knew what was happening—that the stillbirth rate was stable, but that the number of "monstrosities" had increased. She called attention to Dr. M. J. Pleydell's article in the *British Medical Journal*† on congenital abnormalities, and the account of how he had had to obtain his material sources, adding her own comment that the time had arrived for comprehensive notification of abnormalities. This Bill was consequential on the 1956 report on *The Hazards to Man of Nuclear and Allied Radiations*.‡ Every scientist who read the Bill would know its import precisely.

The MINISTER OF HEALTH rebutted the main charge. The studies which the Medical Research Council was making would be assisted by the wider information that was to be obtained (the age of the father and the length of pregnancy). The proportion of mutational births was very small, but in a modern society the question of radiation became more important and was something that should be studied. Dr. SUMMERSKILL was not satisfied. "Why has this whole aspect been evaded?" she asked. "The Minister has accepted it now. He has spoken about mutational births. . . . He admits that its real purpose is related to radioactivity." Mr. WALKER-SMITH.—Obviously that is not the whole purpose of the Bill. The system of collecting the statistics and having them available for scientific study dates back to 1938. It is of great value in all sorts of ways, quite apart from the more specialized use she has been discussing.

Legal Aid to be Extended

The Legal Aid Bill got its second reading on the same day after much longer debate but no such sharp controversy. Its purpose is to widen the scope of the 1949 legislation by

†*British Medical Journal*, January 30, p. 309.
‡*Cmd.* 9780, 1956. H.M.S.O., London.

raising the limits of disposable income from £420 to £700 a year, and the upper limit for free aid from £156 to £275 a year.

Professions Supplementary to Medicine

The Radioactive Substances Bill has only begun the committee stage in the Lords. That of the Professions Supplementary to Medicine Bill has been completed by the Commons in two sessions. The Bill has emerged with two or three simple amendments, and of course without its subpoena powers in the disciplinary provisions. This is the direct consequence of the appointment of the Simonds Committee§ on the evidence produced before disciplinary tribunals, and the future stages of the Bill may suffer some delay until the report is available.

QUESTIONS IN THE COMMONS

"Preludin" on Prescription

The HOME SECRETARY stated on February 4 that he had received from the Poisons Board a report (foreshadowed by the Minister of Health the previous week) containing a recommendation that a number of substances including "preludin" should be supplied only on prescription. "Subject to the consideration of any representations by those concerned," he stated, "I propose to accept this recommendation and to give it effect as soon as practicable."

Safer Domestic Gas

Mr. F. ALLAUN (Salford, East, Lab.) asked the Minister of Power on February 1 to give a general direction to gas boards to accelerate the use of non-toxic gas. Mr. J. C. GEORGE, the Parliamentary Secretary, said that modern processes for making gas from both oil and coal produced gas of low toxicity. The problem of reducing carbon monoxide in gas from older plant was a difficult one which was being urgently pursued, and no general direction was necessary.

Mr. ALLAUN admitted that the completely non-toxic gas produced at Basle was very expensive, but suggested that gas could be produced with a sufficiently low proportion of carbon monoxide to avoid injury. How long would it take to put into effect the recommendations of the Institution of Gas Engineers, which the Gas Council accepted? Mr. GEORGE explained that several methods were known for reducing toxicity, but their use would involve a substantial increase in gas prices and new capital commitments. The modification of existing plant would take many years. The Gas Council was seeking a more economical method, and its research department was actively engaged in examining one of the three methods with a view to improvement and to making it an economical proposition.

World Refugee Year

Mr. D. PRICE (Eastleigh, Con.) asked the Home Secretary on February 2 whether, in pursuance of the support of the World Refugee Year, he would admit another 1,000 refugees to this country before Easter. Mr. BUTLER stated that arrangements were being made in consultation with the United Kingdom Committee of the World Refugee Year to ascertain the number of specially handicapped refugees who wished to come to this country and could be adequately sponsored by the voluntary organizations. He would consider the matter further when this information was available.

On February 5 Mr. J. BIGGS-DAVISON (Chigwell, Con.) asked the Home Secretary the estimated number of tubercular and other hard-core refugees to be admitted to the United Kingdom during World Refugee Year; and the arrangements for their reception and settlement. Mr. BUTLER.—Two hundred refugees, including eighteen suffering from tuberculosis, as well as others with a past history of this disease, have so far been accepted for admission during World Refugee Year. Mr. Butler referred also to his earlier replies to Mr. C. CHATAWAY (Lewisham, North, Con.) on October 30 and to Mr. PRICE.

§See *British Medical Journal*, December 26, p. 1491.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 23** (No. 3) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	6	2	0	0	5	4	1	8	0	3
Dysentery	864	111	219	10		1,194	79	144	18	2
Encephalitis, acute	3	0		0		1	0		0	
Enteric fever:										
Typhoid	0	0	0	0		1	0	1	0	
Paratyphoid	3	0	0	0	1(B)	43	0	0	0	
Food-poisoning	192	21	11	4		200	21	11	0	
Infective enteritis or diarrhoea under 2 years				13	20				12	18
Measles*	1,669	16	32	8	9	13,709	983	341	172	722
Meningococcal infection	18	1	8	0	2	40	2	14	0	2
Ophthalmia neonatorum	32	5	4	0		19	5	4	0	
Pneumonia†	341	25	251	15	4	611	47	454	11	
Poliomyelitis, acute:										
Paralytic	4	0	0	0	1	14	0	3	1	1
Non-paralytic	1	0	0			4	0			
Puerperal fever§	196	33	9	1	1	253	35	17	4	1
Scarlet fever	1,188	39	105	24	14	1,428	79	103	14	34
Tuberculosis:										
Respiratory	449	52	70	23		476	51	88	15	
Non-respiratory	54	3	4	10		67	5	9	3	
Whooping-cough	882	89	196	12	101	658	24	98	102	92

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	1
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		1			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	1	1	0	11	0	1	1	1
Influenza	32	2	1	0	1	55	5	2	2	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia	763	57	33	19	14	875	80	40	18	15
Poliomyelitis, acute	1	0		0	0	2	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	81	2	7	0	3	100	4	20	3	2
Non-respiratory		0	0	0	0		0	1	1	1
Whooping-cough	1	0	0	0	0	1	0	0	1	0
Deaths 0–1 year	335	27	41	5	15	448	46	48	9	9
Deaths (excluding stillbirths)	12,249	940	711	160	175	13,684	1097	894	180	215
LIVE BIRTHS	14,576	1193	1003	241	263	15,435	1284	1179	252	373
STILLBIRTHS	303	26	31			303	22	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Influenza in England and Wales

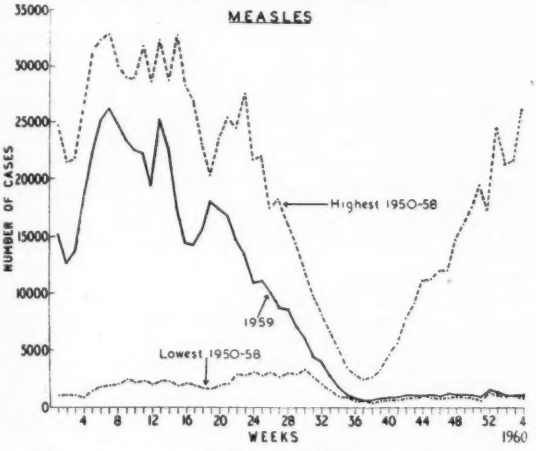
The number of deaths from influenza has risen from 12 in the week ending December 26, 1959, to 43 (22 of them in people over 75) in the week ending January 30, 1960. These figures are smaller than for the corresponding period last year. Deaths from pneumonia have also risen, to 766 in the week ending January 30, 1960; a year before, the figure was 817. Bronchitis deaths in the same week, at 718, were more than 25% fewer than in 1959. Since the beginning of 1960 the new claims on the Ministry of Pensions and National Insurance have been running at a rather lower figure than over the same period in 1959.

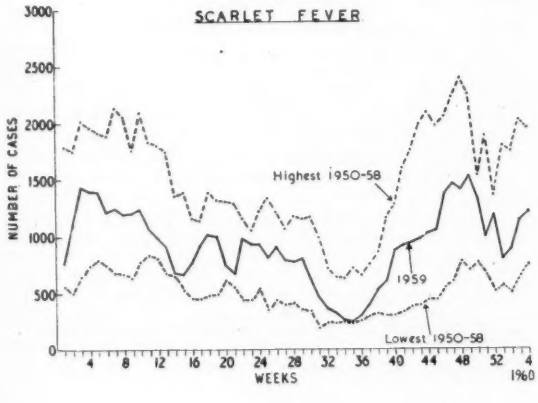
Births in Birmingham

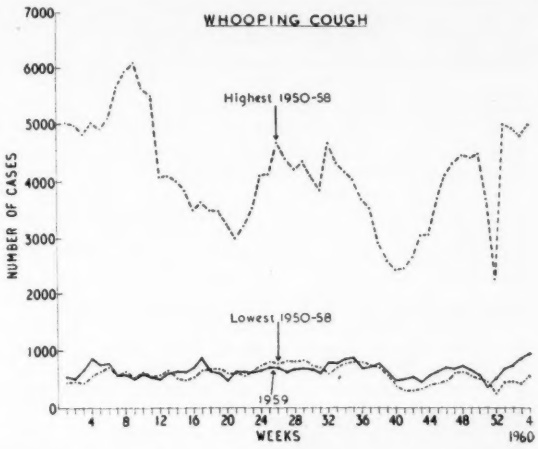
Birmingham mothers gave birth to 18,906 live babies in 1957. Mothers in the age group 25–29 scored the largest total—5,616. Women over 40 contributed 660 babies to the grand total, and 35 babies were born to women of 45 or over. The neonatal mortality rate of babies born to all Birmingham mothers was 17.1. In babies born to mothers aged 40 and over it was 33.5.—*City of Birmingham—Abstract of Statistics,* Number Five, 1958–9.

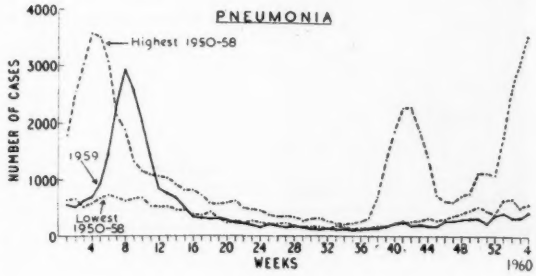
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus - - - - - -, the figures for 1959–60 thus ———. Except for the curves showing notifications in 1959–60, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Jan. 23	Week Ending Jan. 30
Measles		
Devonshire	87	**115**
Exeter C.B.	46	**59**
Lancashire	206	**279**
Liverpool C.B.	46	**61**
Salford C.B.	34	**50**
Dysentery		
Durham	16	**26**
Sunderland C.B.	0	**12**
Essex	8	**41**
Lancashire	187	**343**
Oldham C.B.	22	**106**
Chadderton U.D.	0	**15**
Crompton U.D.	10	**16**
Lees U.D.	0	**18**
Ormskirk U.D.	0	**10**
Swinton and Pendlebury U.D.	2	**33**
Worsley U.D.	8	**11**
Northamptonshire	23	**41**
Corby U.D.	21	**38**
Nottinghamshire	20	**34**
Southwell R.D.	0	**19**
Surrey	10	**33**
Farnham U.D.	5	**13**
Glasgow	121	**152**
Paratyphoid Fever		
Bedfordshire	0	**4**
Luton M.B.	0	**4**
Food-poisoning		
Glamorganshire	0	**30**
Ogmore and Garw U.D.	0	**26**

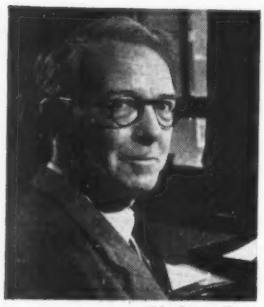
Medical News

Chairman of Clinical Research Board

The Medical Research Council, after consultation with the Ministry of Health and the Department of Health for Scotland, have recently appointed Professor E. J. WAYNE (regius professor of practice of medicine in the University of Glasgow) to be chairman of the Clinical Research Board in succession to Sir GEOFFREY JEFFERSON, who has retired after a six-year term of service as first chairman of the Board.

Waynflete Professor of Physiology, Oxford University

Sir LINDOR BROWN, F.R.S., Jodrell professor of physiology at University College, London, has been appointed Waynflete professor of physiology at Oxford from October 1 in succession to Professor E. G. T. LIDDELL, F.R.S., who is retiring.



J. Carter Fea

He graduated in medicine from Manchester University in 1928, going to the University of Leeds as lecturer in physiology from 1928 to 1934. He joined the National Institute for Medical Research in 1934 and worked there in Sir HENRY DALE'S Laboratory on the chemical transmission of nerve impulses. He was a member of the Medical Research Council itself from 1951 to 1955. During the last war he served as secretary of the Royal Navy Personnel Research Committee, receiving a C.B.E. for his services in 1947. He succeeded Professor LOVATT EVANS as Jodrell professor in 1949, was knighted in 1957, and is now one of the vice-presidents of the Royal Society and its biological secretary.

M.R.C. Fellowships in Clinical Research

The Medical Research Council invite applications for a further series of Fellowships in clinical research tenable at centres in the United Kingdom during the academic year 1960–1. These Fellowships are open to suitably qualified medical or dental graduates who are British subjects resident in the United Kingdom and who desire to prepare themselves for a career in clinical research.

Details and application forms may be obtained from the Secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1, to whom applications should be sent as soon as possible, in any event not later than March 15.

Two London University Chairs

Dr. H. O. SCHILD, reader in pharmacology at University College, has been appointed to the University chair of pharmacology tenable there from October 1, 1961. Dr. Schild is joint author of the revised edition of *Clark's Applied Pharmacology, 1952*. Dr. W. F. WIDDAS, reader in physiology at King's College, has been appointed to the University chair of physiology tenable at Bedford College from October 1 this year.

Supplementary Estimate for Health Services

The supplementary estimate of the amount required in the year ending March 31, 1960, for the national health services for England and Wales and allied services is £23,586,640.

Of this sum salary and wage increases in the Regional Hospital Boards account for £11,917,000, the increased demand for poliomyelitis vaccine for £1,578,200, and an increase in the number and cost of prescriptions for £5,312,000. (*1959–60 Supplementary Estimate: Civil Estimates and Estimates for Revenue Departments*, H.M.S.O., price 9s. 6d.)

Doctors' Window, Guildford Cathedral

At a meeting of the Guildford Division on February 11, Dr. G. I. WATSON, chairman of the Doctors' Cathedral Window Fund, handed to Miss E. IREDALE, O.B.E., secretary of the Guildford New Cathedral Council, a cheque for £1,000 for the doctors' window in the Cathedral.

The Society of Apothecaries, who contributed 55 cheques totalling £268, was represented by its secretary, Mr. E. BUSBY; Dr. D. HEDGCOCK represented the headquarters of the British Medical Association, which contributed £105 centrally and a further £40 from the Surrey divisions. Medical staffs of London teaching hospitals contributed £143, while gifts from other corporate bodies totalled £104. Donations from 352 individual doctors at home and overseas amounted to £642. Miss MOIRA FORSYTH, who made the window, was thanked on behalf of the medical profession by Dr. S. KEYS, Chairman of the Division. The stained glass panels, a photograph of which was published in the *Journal*, April 25, 1959, p. 1130, are now on display at the Cathedral.

B.M.A. Chief Press Officer

Mr. PAUL VAUGHAN, M.A., a graduate of Oxford University, has been appointed Chief Press Officer to the British Medical Association.

Mr. Vaughan joined the B.M.A. in 1955 as senior assistant to the Public Relations Officer, Mr. JOHN PRINGLE, who resigned last autumn. He published *Doctors' Commons*, a short history of the B.M.A. intended for the lay reader, last October.

Anglo-Polish Exchange Scheme

The Polish Medical Association is willing to arrange for a party of about 12 British doctors to visit Poland in May or September, 1961, in exchange for a return visit of Polish doctors to the United Kingdom in 1962. Doctors who are interested are asked to apply to the Secretary, B.M.A. House, Tavistock Square, London, W.C.1.

The visit to Poland would last for two to four weeks. Each individual would pay his own travelling expenses, but board and lodging would be provided by the host doctors. Interpreters would be available, though most Polish doctors know some English. The names of applicants and their special interests would be passed to the Polish Medical Association in Warsaw.

T.A. Senior Medical Unit's Historic Silver

The historic silver of the Territorial Army's oldest medical unit is in need of repair. It includes a challenge shield presented in c. 1885 by, among others, Sir William Jenner and Sir James Paget; and one given by Sir James Cantlie, the surgeon, who in 1883 founded the Volunteer Medical Staff Corps, one of the ancestors of the present unit. The sum of £25 has already been contributed towards the cost of renovation, but a further £25 is still needed. Former members of the unit or other well-wishers are invited to send contributions, however small, to Lieutenant-Colonel M. HATTON, 167 (City of London) Field Ambulance R.A.M.C./T.A., 57a, Farringdon Road, London, E.C.1.

Mental Health Year

World Mental Health Year, 1960, will include in this country a Mental Health Week from July 9 to 16, during which it is hoped that hospitals and other centres will arrange open days. Various constituent bodies of the National Association for Mental Health will organize conferences, and in August the Scottish Association will act as hosts to the annual meeting of the World Federation for Mental Health in Edinburgh.

National Fund for Poliomyelitis Research

The National Fund for Poliomyelitis Research has enlarged its title to the National Fund for Research into Poliomyelitis and Other Crippling Diseases, and the council announces that it is willing to consider applications for grants in connexion with research work coming under this description. Poliomyelitis research will, however, continue to have overriding priority in the work financed by the Fund.

It is not the intention of the Fund to finance work in fields in which substantial sums have already been made available, and, when other interested organizations are known to exist, grants will be made only in agreement with such organizations. The fact that an application comes from overseas will not in itself be a bar to consideration by the Council. The National Fund announces that Lord HARDING OF PETHERTON has been elected chairman of the Fund in the place of Admiral Sir CHARLES DANIEL, who has resigned.

Medical School Cricket Club to Tour Caribbean

This year St. George's Hospital Medical School Cricket Club is planning a playing tour of the British Caribbean Territories during May. The club believes that the tour will be the first of its kind made by any medical school in the United Kingdom, and hopes that the final match will be against the University College of the West Indies (Jamaica). An appeal to business firms for funds to finance the tour is being made by the club's honorary secretary, Mr. LEROY D. FRANKLIN.

Imperial Cancer Research Fund

Lord SALISBURY has agreed to succeed the late Lord HALIFAX as President of the Fund.

COMING EVENTS

Croonian Lectures.—Professor D. E. DENNY-BROWN: "Diseases of the Basal Ganglia and their Relation to Disorders of Movement." For details see *Journal*, advertisement p. 70.

Exhibition of Soviet Books and Periodicals.—Royal Festival Hall, till February 19, 2–10 p.m. Mounted by the British Council on behalf of the Soviet Ministry of Culture. Admission free.

Hunterian Society Oration.—Mr. C. ROBERT RUDOLF: "New Light on William Clift and his Contemporaries," Mansion House, February 22, 8.30 p.m.

University College Hospital: Lecture Demonstrations for General Practitioners.—Conducted by Dr. D. A. POND: "New Stimulants and Tranquillizers in Psychiatry." Sunday, March 6, 10.15 a.m., Front Hall, main hospital. Admission free without ticket.

Society of Chemical Industry: Microbiology Group.—Symposium: "Continuous Culture of Micro-organisms," March 31, April 1, University College, Gower Street, London, W.C.1. Details from the Society, 14, Belgrave Square, London, S.W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, February 15

GUY'S HOSPITAL: PHYSIOLOGY THEATRE.—5.30 p.m., endocrine demonstration: Virilism.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. Ackner: Diagnosis of Organic Confusional States.

UNIVERSITY COLLEGE LONDON: COMMUNICATION RESEARCH CENTRE.—At Physics Theatre, Gower Street, W.C., 5.30 p.m., public lecture by Professor W. G. Hellinga (Amsterdam): Speech of Deaf Children.

Tuesday, February 16

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor C. H. Gray: Non-pancreatic Aspects of Diabetes Mellitus.

GROUP FOR REPRESENTATION OF THE VIEWS OF CLINICAL PSYCHIATRISTS.—At Rygate Room, Tavistock House North (Fourth Floor), Tavistock Square, W.C., 5.30 p.m., meeting.

ILFORD MEDICAL SOCIETY.—At King George Hospital, Ilford, 8.45 p.m., Mr. A. Lawrence Abel: Recent Advances in the Diagnosis and Treatment of Cancer.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. J. W. D. Bull: Radiological Investigation of Strokes.

OSLER CLUB OF LONDON.—At Wellcome Building, Euston Road, N.W., 8 p.m., Dr. Kenneth Dewhurst and Professor G. E. Trease: Thomas Dover (Born 1660).

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Ophthalmology Lecture by Professor A. Sorsby: Optical Components During the Growth of the Eye.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Lecture Theatre, 5 p.m., Mr. J. Suchet: Appraisal of the Results of Treatment of Infertility.

SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, 8.30 p.m., Dr. R. Ewing Rodgers: Demonstration of Medical Cases.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. A. D. Gordon: Ultra-sonic Rays in Neurosurgery.

Wednesday, February 17

EUGENICS SOCIETY.—At 26, Portland Place, W., 5 p.m., Galton Lecture for 1960 by Dr. Eliot Slater: Galton's Heritage.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Pigmented Lesions of the Skin.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. J. R. Belcher: Surgical Treatment of Lung Cancer.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. J. D. Fergusson: Cysts of the Kidneys.

LISTERIAN SOCIETY.—At Lecture Theatre, King's College Hospital Medical School, 8.30 p.m., Mr. A. L. Bacharach, F.R.I.C.: Language—Servant and Master.

●LIVERPOOL UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES.—At Medical School, 8 p.m., Dr. W. H. Taylor: Production of Ascites.

MIDLAND MEDICAL SOCIETY.—At Selly Oak Hospital, 8.15 p.m., clinical meeting.

PHYSICAL SOCIETY COLOUR GROUP.—At Institute of Ophthalmology, 3.30 p.m., Dr. J. D. Moreland: Colour Discrimination, Field Size, Field Position, and Acceptor Populations; 4.15 p.m., Miss J. Cox: Colour Vision Defects Acquired in Diseases of the Eye.

Thursday, February 18

BRITISH INSTITUTE OF RADIOLOGY: ROENTGEN SOCIETY.—8 p.m., Dr. Sydney Blackman: Rotational Tomography of the Face.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. E. M. Vaughan Williams: Relation Between Contractions and Intracellularly Recorded Potentials in Cardiac Muscle.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., discussion to be opened by Dr. C. A. Clarke: Role of Inheritance in Common Diseases.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., Dr. A. Isaacs: Prospects for a Viral Antibiotic.

LONDON UNIVERSITY.—At King's College, Strand, W.C., 5.30 p.m., special university lecture in pharmacology by Dr. Harris Isbell (U.S.A.): Pharmacology of Opiate Addiction.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Mr. Denis Browne: Orthopaedics of the Foetus.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. M. O. Skelton: Some Pathological Conditions of the Pulmonary Tissues.

ROYAL SOCIETY OF HEALTH.—At Town Hall, West Bromwich, 10.15 a.m., Dr. C. W. D. Cole: Medical Aspects of Atmospheric Pollution; Mr. S. Clayton: Practical Application of the Clean Air Act.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At 26, Portland Place, W., 7.30 p.m., Dr. T. F. Davey: Some Recent Chemotherapeutic Work in Leprosy, with a Discussion of Some of the Problems Involved in Clinical Trials. A discussion will follow.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Maurice Partridge: postgraduate demonstration in psychiatry.

Friday, February 19

BRITISH INSTITUTE OF RADIOLOGY: ROENTGEN SOCIETY.—8 p.m., Radiobiology meeting.

BRITISH TUBERCULOSIS ASSOCIATION.—At 26, Portland Place, W., 5 p.m., meeting in conjunction with Metropolitan Regional Thoracic Societies. Dr. H. J. Trenchard: Tuberculous Infection in Pregnancy and its Relation to Congenital Tuberculosis; Dr. V. U. Lutwyche: Epidemiological Aspects of New Town Development; Dr. F. A. Nash: Tuberculous Infection at Work and Examination of Contacts; Dr. J. Spencer Jones: Public and Mass Radiography; Dr. Hugh Ramsay: An Evaluation of Mass Radiography Methods.

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 4.30 p.m., Radiodiagnosis Section Meeting. Papers by Dr. Ralph Eban, Dr. C. M. Davis, and Dr. F. H. Doyle.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. O. L. S. Scott: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. M. Paneth: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. W. D. Doey: Foreign Bodies in the Ear, Nose, and Throat.

INSTITUTE OF NEUROLOGY.—4.30 p.m., Dr. Macdonald Critchley: History of our Conception as to the Origin of Language in Man—Part I.

LONDON UNIVERSITY.—At Clinical Lecture Theatre, St. Bartholomew's Hospital, 4.45 p.m., special university lecture in medicine by Professor J. Loewenthal (Sydney): Some Contributions to Surgical Research.

PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., joint discussion meeting with Incorporated Law Society of Plymouth: Medicine and the Law.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Professor A. S. Johnstone: Hiatus Hernia. (2) 4 p.m., Dr. J. A. Fraser Roberts: Medical Genetics (I).

ROYAL INSTITUTION.—9 p.m., Professor J. Z. Young, F.R.S.: Eyes, Colours and Shapes.

SOCIETY OF MEDICAL OFFICERS OF HEALTH: WELSH BRANCH.—At B.M.A. House, 195, Newport Road, Cardiff, 6.30 p.m., Dr. Linford Rees: Mental Illness and Pregnancy.

Saturday, February 20

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.—At Hull, 2 p.m., 38th ordinary meeting.

Sunday, February 21

DENTAL AND MEDICAL SOCIETY FOR THE STUDY OF HYPNOSIS.—At Midland Hotel, Manchester, 11 a.m., Dr. Skemp: Freudian Theory and Hypnosis.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Brown.—On January 12, 1960, William Limont Brown, M.B., C.M., of 15, St. Hilda's Terrace, Whitby, Yorks, aged 89.

Coffey.—On January 16, 1960, at Patrickswell, Co. Limerick, Patrick Coffey, L.R.C.P.&S.Ed., L.R.F.P.S., formerly of Harlington, Middlesex, aged 84.

Cullen.—On January 21, 1960, at 76, Oswald Road, Scunthorpe, Lincs, Thomas Cullen, M.B., Ch.B., D.T.M.&H., aged 59.

Dickins.—On January 13, 1960, Sidney John Oldacres Dickins, M.B.E., M.D., of Furzefield House, High Salvington, Worthing, Sussex, and formerly of Cowfold, aged 90.

Dugan.—On January 15, 1960, Douglas Ross Dugan, M.B., Ch.B., of 214, Queens Road, Aberdeen, aged 62.

Farncombe.—On January 15, 1960, at Clare Cottage, Collington Lane, Bexhill, Sussex, Ronald Farncombe, M.R.C.S., L.R.C.P., aged 54.

Harburn.—On January 24, 1960, Mary Harburn, M.B., Ch.B., of 34, Queen Street, Scarborough, aged 57.

Irving.—In January, 1960, Edward Porteous Irving, M.B., Ch.B.

Little.—On January 12, 1960, at Hammersmith Hospital, Paul MacDonald Little, *M.C.*, M.B., Ch.B.Ed., formerly of India.

Milne.—On January 17, 1960, at 4, Shinfield Road, Reading, Berkshire, Robert Bruce Milne, M.B., Ch.B.

Mitchell.—On January 24, 1960, Edward Joseph Mitchell, M.B., Ch.B., D.O., of Sandhurst, Pleasington, near Blackburn, aged 48.

Yates.—On January 15, 1960, at 368, Lees Road, Oldham, James Yates, L.M.S.S.A.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Porphyria in the Elderly

Q.—*An elderly man has suffered intermittently for two years from large bullous lesions on the dorsum of both hands and fingers. Examination of the urine and stool showed large amounts of porphyrins. Is chloroquine beneficial in these cases? Would the blister fluid on aspiration and exposure to Wood's light fluoresce in the same way as the urine?*

A.—The onset of bullous lesions on the backs of the hands and fingers in an elderly man with an abnormally raised urinary and faecal porphyrin suggests acquired porphyria rather than an inborn abnormality. However, Waldenström's porphyria cutanea tarda hereditaria,[1 2] which is familial and inherited as a non-sexlinked dominant trait, may produce symptoms only late in life or merely slight fragility of habitually exposed skin, thus often avoiding early detection.[3] It is at times possible only by investigating faecal and urinary porphyrin excretion of blood relations to differentiate between acquired and familial porphyria. This point is not merely academic because it may lead to the detection of latent and undiagnosed porphyrics.

Chloroquine has been tried in porphyria by a number of physicians, including Woods *et al.*,[4] but apparently without advantage. This is not entirely surprising, because, although skin lesions in porphyria are confined to areas habitually exposed to light, these patients may react subnormally to ultraviolet irradiation.[3 5 6] Chloroquine should perhaps not be used in porphyria because considerable amounts are deposited in the liver, and Linden, Steffen, Newcomer, and Chapman[7] believed that chloroquine precipitated acute intermittent porphyria in a patient with discoid lupus erythematosus.

It is rarely possible to demonstrate in porphyria fluorescence of blister fluid in Wood's light. This may occur, however, whenever the serum shows strong fluorescence.

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4 Woods, S. M., Peters, H. A., and Johnson, S. A. M., *A.M.A. Arch. Derm.*, 1958 **77**, 559.
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6 Wells, G. C., and Rimington, C., *Brit. J. Derm.*, 1953, **65**, 337.
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Action of Amiphenazole

Q.—*Is amiphenazole a circulatory stimulant as well as a respiratory stimulant? Could it be used for long-term therapy in cases of persistent bronchospasm, and would the respiratory centre be uniformly sensitive to it? How is it that the drug causes nausea, but prevents nausea produced by large doses of morphine? Is amiphenazole synergistic with nikethamide?*

A.—There is no conclusive evidence that amiphenazole has a direct stimulant action on the circulatory system. There would appear to be nothing to contraindicate its use together with effective bronchodilator drugs in the long-term therapy of cases of persistent bronchospasm. I cannot quote any work which proves that the respiratory centre remains uniformly sensitive to it when given over prolonged periods of time. However, it has been given with morphine in cases of terminal carcinoma for periods of 4 to 8 months and apparently retained a stimulant effect on the respiratory centre over these periods of time.[1] It is not known how amiphenazole prevents the nausea produced by large doses of morphine. There is no systematic work showing that amiphenazole is synergistic with nikethamide. I should expect, however, that their actions on the respiratory centre would tend to be additive.

REFERENCE

1 McKeogh, J., and Shaw, F. H., *Brit. med. J.*, 1956, **1**, 142.

Sedatives in Pregnancy

Q.—*Could morphine and hyoscine, or intramuscular phenobarbitone, or intramuscular paraldehyde be given without damage to the foetus in a woman in the last three months of pregnancy who became uncontrollable, either from psychotic, psychopathic, or hysterical upsets?*

A.—There is no reason to suppose that any of these drugs in the dosage normally employed could hurt the foetus. In practice, for a patient who is "uncontrollable," 10 ml. of paraldehyde would act quickly and more effectively than the others.

Congenital Deformity of Leg

Q.—*A woman had a congenital abnormality consisting of an absence of fibula, a much shortened tibia, and a deformed foot with only the medial three toes present. Amputation was necessary. No similar deformity or abnormality can be traced in four generations of her or her husband's family. Is there any possibility of a hereditary tendency?*

A.—There is a possibility that the patient might have been affected by a dominant mutation, but the possibility is remote. So far as I know, this malformation has not been reported in more than one member of a family.

Testing Vision by "Ortho-rater"

Q.—*Would an "ortho-rater" be helpful in the selection of personnel for special visual inspection work?*

A.—The ortho-rater is essentially a stereoscope so designed that visual acuity for near and distance, muscle balance, colour vision and depth perception can be recorded by a lay operator. Its main application is for screening large numbers of people to detect those requiring further examination by an ophthalmologist. For further details of this and other instruments see Weston.[1] If the inspection work mentioned in the question requires higher than average standards of vision and applies to a limited number of people, it might be better to use special tests designed to simulate the actual working conditions.

REFERENCE

1 Weston, H. C., *Sight, Light and Efficiency*, 1949. Lewis, London.

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